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(54) **Title:** ANTISENSE MODULATION OF ENDOTHELIAL SPECIFIC MOLECULE 1 EXPRESSION

(57) **Abstract:** Antisense compounds, compositions, and methods are provided for modulating the expression of Endothelial Specific Molecule-1 (ESM-1). The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding ESM-1. Methods of using these compounds for modulation of ESM-1 expression and for treatment of diseases associated with expression of ESM-1 are provided.

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ANTISENSE MODULATION OF ENDOTHELIAL SPECIFIC MOLECULE 1 EXPRESSION

The present application claims priority under Title 35, United States Code, §119 to United States Provisional application Serial No. 60/404,495, filed August 19, 2002, which is incorporated by reference in its entirety as if written herein.

FIELD OF THE INVENTION

[001] The present invention provides compositions and methods for modulating the expression of Endothelial Specific Molecule-1 (ESM-1). In particular, this invention relates to antisense compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding Endothelial Specific Molecule-1. Such oligonucleotides have been shown to modulate the expression of Endothelial Specific Molecule-1.

BACKGROUND OF THE INVENTION

[002] Angiogenesis is the growth of new capillary blood vessels from pre-existing vessels and capillaries and is crucial in a large number of processes, such as wound repair, embryonic development, and the growth of solid tumors. In neovascularization, endothelial cells will undergo migration, elongation, proliferation, and orientation leading to lumen formation, re-establishment of a basement membrane and eventual anastomosis with other vessels (Patan S. et al., (2000), *J. Neurooncol.* **50**: 1-15).

[003] Endothelial cell-specific molecule1 (ESM-1) was originally isolated in an immunoscreening of a HUVEC cDNA library in order to identify the gene encoding a 55-kDa autoantigen that may have a role in asthma (Lassalle, P., et al.,). The full length ESM-1 cDNA was cloned in a library constructed in pCDM8 but was found to be inserted in the reverse orientation (Lassalle, P., et al.,).

[004] Northern blots have shown ESM-1 to probes to hybridize to RNA from HUVEC cells, SV40-transfected HUVECs, human lung, and human kidney. Little or none was detected in human heart, pancreas, placenta, muscle, brain or liver (Lassalle et al., 1996). Antibodies raised to ESM-1 show protein expression in human lung, colon, and kidney (Bechard, D., et al.,. (2000). *J. Vasc. Res.* **37**, 417-425; WO9945028). In the lung, ESM-1 is expressed in venules, arterioles, and alveolar capillaries as well as by epithelial cells of the bronchi and submucosal glands. In the kidney, expression is predominantly in renal tubular epithelial cells. Capillaries and venules of the lamina propria of the colon also display ESM-1 expression. A splice variant of ESM-1 has been identified which lacks 150 base pairs but maintains the open reading frame (Aitkenhead, M., et al., (2002) *Microvasc. Res.* **63**, 159-171).

[005] ESM-1 expression appears to be both constitutive and under the control of a variety of cytokines. HUVEC cells treated with TNFα or IL-1βdisplay an up-regulation of the gene. No change in ESM-1 levels was seen upon treatment with IL-4 or IFNγ. While coadministration of TNFα and IFNγ lead to a synergistic induction of proinflammatory factors such as IL-6, IL-8, RANTES and ICAM-1, the combination of these two cytokines inhibit the TNFα induced ESM-1 up-regulation (Lassale et al., 1996).

[006] ESM-1 has been found to be differentially expressed in endothelial cells forming tubes in a 3-dimensional collagen gel when compared to cells growing in two dimensions (Aitkenhead et al., 2002). Microarray analysis indicates a higher level of ESM-1 expression in HMVEC cells growing on collagen relative to those growing on osteopontin. We followed up on this observation by investigating the expression level of ESM-1 in colon tumor samples compared to a pool of normal colon tissue. Nine of ten tumors showed expression at levels of threefold or higher at the RNA level, as determined by real-time quantitative reverse transcription polymerase chain reaction experiments.

[007] We have amplified ESM-1 from HDMECs and cloned it into an expression vector. A pool of transfected NIH3T3 cells were then selected and assayed for ESM-1 expression. After confirming significant gene over-expression at the RNA level, cells were injected subcutaneously into a nu/nu female mouse. While vector transfected NIH3T3 fibroblasts failed to grow in these mice, those cells transfected with ESM-1 formed solid tumors within three weeks. This data shows that ESM-1 contains the potential to augment growth *in vivo* to a cell line that is usually not capable of forming tumors.

[008] Previous work on ESM-1 has found that levels of expression of this gene change in cells under varying conditions. We have extended those findings to show that ESM-1 is up regulated in colon carcinomas when compared to normal colon tissue. Additionally, we have shown that forced over-expression of ESM-1 leads to an escalation of growth of NIH3T3 fibroblasts *in vivo*.

[009] Antisense technology is emerging as an effective means for reducing the expression of specific gene products and may therefore prove to be uniquely useful in a number of therapeutic, diagnostic, and research applications for the modulation of ESM-1 expression.

SUMMARY OF THE INVENTION

[0010] The present invention is directed to antisense compounds, particularly oligonucleotides, which are targeted to a nucleic acid encoding ESM-1, and which modulate the expression of ESM-1. Pharmaceutical and other compositions comprising the antisense compounds of the invention are also provided. Further provided are methods of modulating the expression of ESM-1 in cells or tissues comprising contacting said cells or tissues with one or more of the antisense compounds or compositions of the invention. Further provided are methods of treating an animal, particularly a human, suspected of having or being prone to a disease or condition associated with

expression of ESM-1 by administering a therapeutically or prophylactically effective amount of one or more of the antisense compounds or compositions of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0011] Figure 1 shows the cDNA sequence and the ESM-1 protein sequence encoded therefrom.

[0012] Figure 2 shows the ESM-1 expression levels in ten tumors as determined by Real-Time Quantitative PCR.

DETAILED DESCRIPTION OF THE INVENTION

[0013] The present invention employs oligomeric antisense compounds, particularly oligonucleotides, for use in modulating the function of nucleic acid molecules encoding ESM-1, ultimately modulating the amount of ESM-1 produced. This is accomplished by providing antisense compounds, which specifically hybridize with one or more nucleic acids encoding ESM-1. As used herein, the terms "target nucleic acid" and "nucleic acid encoding ESM-1" encompass DNA encoding ESM-1, RNA (including pre-mRNA and mRNA) transcribed from such DNA, and also cDNA derived from such RNA. The specific hybridization of an oligomeric compound with its target nucleic acid interferes with the normal function of the nucleic acid. This modulation of function of a target nucleic acid by compounds, which specifically hybridize to it, is generally referred to as "antisense". The functions of DNA to be interfered with include replication and transcription. The functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such

interference with target nucleic acid function is modulation of the expression of ESM-1. In the context of the present invention, "modulation" means either an increase (stimulation) or a decrease (inhibition) in the expression of a gene. In the context of the present invention, inhibition is the preferred form of modulation, of gene expression and mRNA is a preferred target.

[0014] It is preferred to target specific nucleic acids for antisense. "Targeting" an antisense compound to a particular nucleic acid, in the context of this invention, is a multistep process. The process usually begins with the identification of a nucleic acid sequence whose function is to be modulated. This may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. In the present invention, the target is a nucleic acid molecule encoding ESM-1. The targeting process also includes determination of a site or sites within this gene for the antisense interaction to occur such that the desired effect, e.g., detection or modulation of expression of the protein, will result. Within the context of the present invention, a preferred intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame (ORF) of the gene. Since, as is known in the art, the translation initiation codon is typically 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is also referred to as the "AUG codon," the "start codon" or the "AUG start codon". A minority of genes have a translation initiation codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and 5'-AUA, 5'-ACG and 5'-CUG have been shown to function in vivo. Thus, the terms "translation initiation codon" and "start codon" can encompass many codon sequences, even though the initiator amino acid in each instance is typically methionine (in eukaryotes) or formylmethionine (in prokaryotes). It is also known in the art that eukaryotic and prokaryotic genes may have two or more alternative start codons, any one of which may be preferentially utilized for translation

initiation in a particular cell type or tissue, or under a particular set of conditions. In the context of the invention, "start codon" and "translation initiation codon" refer to the codon or codons that are used in vivo to initiate translation of an mRNA molecule transcribed from a gene encoding ESM-1, regardless of the sequence(s) of such codons.

[0015] It is also known in the art that a translation termination codon (or "stop codon") of a gene may have one of three sequences, i.e. 5'-UAA, 5'-UAG and 5'-UGA (the corresponding DNA sequences are 5'-TAA, 5'-TAG and 5'-TGA, respectively). The terms "start codon region" and "translation initiation codon region "refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation codon. Similarly, the terms "stop codon region" and "translation termination codon region "refer to a portion of such an mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation termination codon.

[0016] The open reading frame (ORF) or "coding region," which is known in the art to refer to the region between the translation initiation codon and the translation termination codon, is also a region which may be targeted effectively. Other target regions include the 5' untranslated region (5'UTR), known in the art to refer to the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene, and the 3' untranslated region (3'UTR), known in the art to refer to the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene. The 5' cap of an mRNA comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage. The 5' cap region of an mRNA is considered to include the 5'

cap structure itself as well as the first 50 nucleotides adjacent to the cap. The 5' cap region may also be a preferred target region.

[0017] Although some eukaryotic mRNA transcripts are directly translated, many contain one or more regions, known as "introns," which are excised from a transcript before it is translated. The remaining (and therefore translated) regions are known as "exons" and are spliced together to form a continuous mRNA sequence. mRNA splice sites, i.e., intron-exon junctions, may also be preferred target regions, and are particularly useful in situations where aberrant splicing is implicated in disease, or where an overproduction of a particular mRNA splice product is implicated in disease. Aberrant fusion junctions due to rearrangements or deletions are also preferred targets. It has also been found that introns can also be effective, and therefore preferred, target regions for antisense compounds targeted, for example, to DNA or pre-mRNA.

[0018] Once one or more target sites have been identified, oligonucleotides are chosen which are sufficiently complementary to the target, i.e., hybridize sufficiently well and with sufficient specificity, to give the desired effect.

[0019] In the context of this invention, "hybridization" means hydrogen bonding, which may be Watson-Crick, Hoogsteen, or reversed Hoogsteen hydrogen bonding, between complementary nucleoside or nucleotide bases. For example, adenine and thymine are complementary nucleobases, which pair through the formation of hydrogen bonds. "Complementary," as used herein, refers to the capacity for precise pairing between two nucleotides. For example, if a nucleotide at a certain position of an oligonucleotide is capable of hydrogen bonding with a nucleotide at the same position of a DNA or RNA molecule, then the oligonucleotide and the DNA or RNA are considered to be complementary to each other at that position. The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus,

"specifically hybridizable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable. An antisense compound is specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

[0020] Antisense compounds are commonly used as research reagents and diagnostics. For example, antisense oligonucleotides, which are able to inhibit gene expression with exquisite specificity, are often used by those of ordinary skill to elucidate the function of particular genes. Antisense compounds are also used, for example, to distinguish between functions of various members of a biological pathway. Antisense modulation has, therefore, been harnessed for research use.

[0021] The specificity and sensitivity of antisense is also harnessed by those of skill in the art for therapeutic uses. Antisense oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. Antisense oligonucleotides have been safely and effectively administered to humans and numerous clinical trials are presently underway. It is thus established that oligonucleotides can be useful therapeutic modalities that can be configured to be useful in treatment regimes for treatment of cells, tissues and animals, especially humans. In the context of this invention, the term "oligonucleotide" refers to an oligomer or polymer

of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or mimetics thereof. This term includes oligonucleotides composed of naturally occurring nucleobases, sugars and covalent internucleoside (backbone) linkages as well as oligonucleotides having non-naturally occurring portions which function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

[0022] ESM-1 antisense oligonucleotides that have activity in the cardiovascular, angiogenic, and endothelial assays described herein, and/or whose gene product has been found to be localized to the cardiovascular system, is likely to have therapeutic uses in a variety of cardiovascular, endothelial, and angiogenic disorders, including systemic disorders that affect vessels, such as diabetes mellitus. Its therapeutic utility could include diseases of the arteries, capillaries, veins, and/or lymphatics. Examples of treatments hereunder include treating muscle wasting disease, treating osteoporosis, aiding in implant fixation to stimulate the growth of cells around the implant and therefore facilitate its attachment to its intended site, increasing IGF stability in tissues or in serum, if applicable, and increasing binding to the IGF receptor (since IGF has been shown in vitro to enhance human marrow erythroid and granulocytic progenitor cell growth).

[0023] ESM-1 antisense oligonucleotides can be used to inhibit the production of excess connective tissue during wound healing or pulmonary fibrosis if ESM-1 promotes such production. This would include treatment of acute myocardial infarction and heart failure.

[0024] Moreover, the present invention provides the treatment of cardiac hypertrophy, regardless of the underlying cause, by administering a therapeutically effective dose of ESM-1 antisense oligonucleotides.

[0025] The treatment for cardiac hypertrophy can be performed at any of its various stages, which may result from a variety of diverse pathologic conditions, including myocardial infarction, hypertension, hypertrophic cardiomyopathy, and valvular regurgitation. The treatment extends to all stages

of the progression of cardiac hypertrophy, with or without structural damage of the heart muscle, regardless of the underlying cardiac disorder.

[0026] ESM-1 antisense oligonucleotides would be useful for treatment of disorders where it is desired to limit or prevent angiogenesis. Examples of such disorders include vascular tumors such as hemangioma, tumor angiogenesis, neovascularization in the retina, choroid, or cornea, associated with diabetic retinopathy or premature infant retinopathy or macular degeneration and proliferative vitreoretinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, ovarian hyperstimulation, psoriasis, endometriosis associated with neovascularization, restenosis subsequent to balloon angioplasty, sear tissue overproduction, for example, that seen in a keloid that forms after surgery, fibrosis after myocardial infarction, or fibrotic lesions associated with pulmonary fibrosis.

[0027] Specific types of diseases are described below, where ESM-1 antisense oligonucleotides may serve as useful for vascular- related drug targeting or as therapeutic targets for the treatment or prevention of the disorders.

[0028] Atherosclerosis is a disease characterized by accumulation of plaques of intimal thickening in arteries, due to accumulation of lipids, proliferation of smooth muscle cells, and formation of fibrous tissue within the arterial wall. The disease can affect large, medium, and small arteries in any organ. Changes in endothelial and vascular smooth muscle cell function are known to play an important role in modulating the accumulation and regression of these plaques.

[0029] Hypertension is characterized by raised vascular pressure in the systemic arterial, pulmonary arterial, or portal venous systems. Elevated pressure may result from or result in impaired endothelial function and/or vascular disease.

[0030] Inflammatory vasculitides include giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa (including the microangiopathic form), Kawasaki's disease, microscopic polyarightis, Wegener's granulomatosis, and a variety 101 of infectious-related vascular disorders (including Henoch-Schonlein Prupura). Altered endothelial cell function has been shown to be important in these

diseases. Reynaud's disease and Reynaud's phenomenon are characterized by intermittent abnormal impairment of the circulation through the extremities on exposure to cold. Altered endothelial cell function has been shown to be important in this disease.

[0031] Aneurysms are saccular or fusiform dilatations of the arterial or venous tree that are associated with altered endothelial cell and/or vascular smooth muscle cells.

[0032] Arterial restenosis (restenosis of the arterial wall) may occur following angioplasty as a result of alteration in the function and proliferation of endothelial and vascular smooth muscle cells.

[0033] Thrombophlebitis and lymphangitis are inflammatory disorders of veins and lymphatics, respectively, that may result from, and/or in, altered endothelial cell function. Similarly, lymphedema is a condition involving impaired lymphatic vessels resulting from endothelial cell function.

[0034] The family of benign and malignant vascular tumors is characterized by abnormal proliferation and growth of cellular elements of the vascular system. For example, lymphangiomas are benign tumors of the lymphatic system that are congenital, often cystic, malformations of the lymphatics that usually occur in newborns.

[0035] Cystic tumors tend to grow into the adjacent tissue. Cystic tumors usually occur in the cervical and axillary region. They can also occur in the soft tissue of the extremities. The main symptoms are dilated, sometimes reticular, structured lymphatics and lymphocysts surrounded by connective tissue.

[0036] Lymphangiomas are assumed to be caused by improperly connected embryonic lymphatics or their deficiency. The result is impaired local lymph drainage.

[0037] Another use for ESM-1 antisense antagonists is in the prevention of tumor angiogenesis, which involves vascularization of a tumor to enable it to growth and/or metastasize. This process is dependent on the growth of new blood vessels. Examples of neoplasms and related conditions that involve tumor angiogenesis include breast carcinomas, lung carcinomas, gastric carcinomas, esophageal carcinomas, colorectal carcinomas, liver carcinomas, ovarian carcinomas, thecomas, arrhenoblastomas, cervical carcinomas, endometrial

carcinoma, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinomas, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinomas, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

[0038] Healing of trauma such as wound healing and tissue repair is also a targeted use for ESM-1 antisense oligonucleotides. Formation and regression of new blood vessels is essential for tissue healing and repair. This category includes bone, cartilage, tendon, ligament, and/or nerve tissue growth or regeneration, as well as wound healing and tissue repair and replacement, and in the treatment of burns, incisions, and ulcers.

[0039] ESM-1 antisense oligonucleotides that induce cartilage and/or bone growth in circumstances where bone is not normally formed have application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing ESM-1 antisense oligonucleotides may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic, resection-induced craniofacial defects, and also is useful in cosmetic plastic surgery.

[0040] It is expected that ESM-1 antisense oligonucleotides may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, or endothelium), muscle (smooth, skeletal, or cardiac), and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate.

[0041] ESM-1 antisense oligonucleotides may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. Also, ESM-1 antisense oligonucleotides may be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells, or for inhibiting the growth of tissues described above.

[0042] ESM-1 antisense oligonucleotides may also be used in the treatment of periodontal diseases and in other tooth-repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells, or induce differentiation of progenitors of bone-forming cells ESM-1 antisense oligonucleotides may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes, since blood vessels play an important role in the regulation of bone turnover and growth.

[0043] Another category of tissue regeneration activity that may be attributable to ESM-1 antisense oligonucleotides is tendon/ligament formation. A protein that induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed has application in the healing of tendon or ligament tears, deformities, and other tendon or ligament defects in humans and other animals. Such a preparation may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of ESM-1 antisense oligonucleotides contributes to the repair of congenital, trauma-induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions herein may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament forming cells, or induce growth of tendon/ligament cells or progenitors ex vivo for return in vivo to effect tissue

repair. The compositions herein may also be useful in the treatment of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

[0044] ESM-1 antisense oligonucleotides may also be administered prophylactically to patients with cardiac hypertrophy, to prevent the progression of the condition, and avoid sudden death, including death of asymptomatic patients. Such preventative therapy is particularly warranted in the case of patients diagnosed with massive left ventricular cardiac hypertrophy (a maximal wall thickness of 35 mm. or more in adults, or a comparable value in children), or in instances when the hemodynamic burden on the heart is particularly strong.

[0045] ESM-1 antisense oligonucleotides may also be useful in the management of atrial fibrillation, which develops in a substantial portion of patients diagnosed with hypertrophic cardiomyopathy. Further indications include angina, myocardial infarctions such as acute myocardial infarctions, and heart failure such as congestive heart failure. Additional non-neoplastic conditions include psoriasis, diabetic and other proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, preeclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion.

[0046] In view of the above, ESM-1 antisense oligonucleotides, which are shown to alter or impact endothelial cell function, proliferation, and/or form, are likely to play an important role in the etiology and pathogenesis of many or all of the disorders noted above, and as such can serve as therapeutic targets to augment or inhibit these processes or for vascular-related drug targeting in these disorders.

Combination Therapies

[0047] The effectiveness of ESM-1 antisense oligonucleotides in preventing or treating the disorder in question may be improved by administering the active agent serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions. For example, for treatment of cardiac hypertrophy, ESM-1 antisense therapy can be combined with the administration of inhibitors of known cardiac myocyte hypertrophy factors, e.g., inhibitors of cc-adrenergic agonists such as phenylephrine; endothelin-1 inhibitors such as BOSENTAN™ and MOXONODIN™; inhibitors to CT- I (US Pat. No. 5,679,545); inhibitors to LIF; ACE inhibitors; des- aspartate-angiotensin I inhibitors (U.S. Pat. No. 5,773,415), and angiotensin II inhibitors.

[0048] For treatment of cardiac hypertrophy associated with hypertension, ESM-1 antisense oligonucleotides can be administered in combination with P-adrenergic receptor blocking agents, e.g., propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol; ACE inhibitors, e.g., quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril; diuretics, e.g., chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or calcium channel blockers, e.g., diltiazem, nifedipine, verapamil, or nicardipine. Pharmaceutical compositions comprising the therapeutic agents identified herein by their generic names are commercially available, and are to be administered following the manufacturers' instructions for dosage, administration, adverse effects, contraindications, etc. 119 See, e.z., *Physicians' Desk Reference* (Medical Economics Data Production Co.: Montvale, N.J., 1997), 51 st Edition. Preferred candidates for combination therapy in the treatment of hypertrophic cardiormyopathy are P-adrenergic-blocking drugs (e.g., propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol), verapamil, difedipine, or diltiazem. Treatment of hypertrophy associated with high blood pressure may require the use of antihypertensive drug therapy, using calcium channel blockers, e.g., diltiazem, nifedipine, verapamil, or nicardipine; P-adrenergic blocking agents; diuretics, e.g., chlorothiazide, hydrochlorothiazide, hydroflumethiazide,

methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or ACE-inhibitors, e. g., quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril.

[0049] For other indications, ESM-1 antisense oligonucleotides may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as EGF, PDGF, TGF- or TGF-, IGF, FGF, and CTGF.

[0050] In addition, ESM-1 antisense oligonucleotides used to treat cancer may be combined with cytotoxic, chemotherapeutic, or growth-inhibitory agents as identified above. Also, for cancer treatment, ESM-1 antisense oligonucleotides are suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

[0051] The effective amounts of the therapeutic agents administered in combination with ESM-1 antisense oligonucleotides thereof will be at the physician's, or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. For example, for treating hypertension, these amounts ideally take into account use of diuretics or digitalis, and conditions such as hyper- or hypotension, renal impairment, etc. The dose will additionally depend on such factors as the type of the therapeutic agent to be used and the specific patient being treated. Typically, the amount employed will be the same dose as that used, if the given therapeutic agent is administered without ESM-1 antisense oligonucleotides.

[0052] For treatment of breast carcinoma, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, Trastuzumab (Herceptin) with chemotherapy, paclitaxel, docetaxel, epirubicin, mitoxantrone, topotecan, capecitabine, vinorelbine, thiotepa, vincristine, vinblastine, carboplatin or cisplatin, plicamycin, anastrozole, letrozole, exemestane, toremifine, or progestins.

[0053] For treatment of acute lymphocytic leukemia, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, doxorubicin, cytarabine, cyclophosphamide, etoposide, teniposide, allopurinol, or autologous bone marrow transplantation.

[0054] For treatment of acute myelocytic and myelomonocytic leukemia, ESM-1, antisense oligonucleotides can be administered in combination with, but not limited to, gemtuzumab ozogamicin (Mylotarg), mitoxantrone, idarubicin, etoposide, mercaptopurine, thioguanine, azacitidine, amsacrine, methotrexate, doxorubicin, tretinoin, allopurinol, leukapheresis, prednisone, or arsenic trioxide for acute promyelocytic leukemia.

[0055] For treatment of chronic myelocytic leukemia, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, busulfan, mercaptopurine, thioguanine, cytarabine, plicamycin, melphalan, autologous bone marrow transplantation, or allopurinol.

[0056] For treatment of chronic lymphocytic leukemia, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, vincristine, cyclophosphamide, doxorubicin, cladribine (2-chlorodeoxyadenosine; CdA), allogeneic bone marrow transplant, androgens, or allopurinol.

[0057] For treatment of multiple myeloma, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, etoposide, cytarabine, alpha interferon, dexamethasone, or autologous bone marrow transplantation.

[0058] For treatment of carcinoma of the lung (small cell and non-small cell), ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, cyclophosphamide, doxorubicin, vincristine, etoposide, mitomycin, ifosfamide, paclitaxel, irinotecan, or radiation therapy.

[0059] For treatment of carcinoma of the colon and rectum, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, capecitabine, methotrexate, mitomycin, carmustine, cisplatin, irinotecan, or floxuridine.

[0060] For treatment of carcinoma of the kidney, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, alpha interferon, progestins, infusional FUDR, or fluorouracil.

[0061] For treatment of carcinoma of the prostate, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to,

ketoconazole, doxorubicin, aminoglutethimide, progestins, cyclophosphamide, cisplatin, vinblastine, etoposide, suramin, PC-SPES, or estramustine phosphate.

[0062] For treatment of melanoma, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, carmustine, lomustine, melphalan, thiotepa, cisplatin, paclitaxel, tamoxifen, or vincristine.

[0063] For treatment of carcinoma of the ovary, ESM-1 antisense oligonucleotides can be administered in combination with, but not limited to, docetaxel, doxorubicin, topotecan, cyclophosphamide, doxorubicin, etoposide, or liposomal doxorubicin.

[0064] While antisense oligonucleotides are a preferred form of antisense compound, the present invention comprehends other oligomeric antisense compounds, including but not limited to oligonucleotide mimetics such as are described below. The antisense compounds in accordance with this invention preferably comprise from about 8 to about 30 nucleobases (i.e. from about 8 to about 30 linked nucleo sides). Particularly preferred antisense compounds are antisense oligonucleotides, even more preferably those comprising from about 12 to about 25 nucleobases. As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to either the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, the phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. In turn the respective ends of this linear polymeric structure can be further joined to form a circular structure, however, open linear structures are generally preferred. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside backbone of the oligonucleotide. The normal I linkage or backbone of RNA and DNA is a 3' to 5' phosphodiester linkage.

[0065] Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural internucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

[0066] Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

[0067] Representative United States patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S.: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, each of which is herein incorporated by reference.

[0068] Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or

more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

[0069] Representative United States patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference.

[0070] In other preferred oligonucleotide mimetics, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., *Science*, 1991, 254, 1497-1500.

[0071] Most preferred embodiments of the invention are oligonucleotides with phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular -CH_2-NH-O-CH_2-, -CH_2-N (CH_3) -O-CH_2- [known as a methylene (methylimino) or MMI backbone], - CH_2-O-N (CH_3) -CH_2-, -CH_2N(CH_3)-N(CH_3)-CH_2- and -O-N(CH_3)-CH_2-CH_2- [wherein the native phosphodiester backbone is represented as -O-P-O-CH_2-] of the above referenced U.S. patent 5,489,677, and the amide backbones of the above referenced U.S. patent 5,602,240. Also preferred are oligonucleotides having morpholino backbone structures of the above-referenced U.S. patent 5,034,506.

[0072] Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Particularly preferred are $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_n$,OCH_3, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_{2n}ON[(CH_2)_nCH_3)]_2$ where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following at the 2' position: C_1 to C_{10}, (lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, $ON0_2$, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2' -methoxyethoxy (2' -O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and

2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH_2-O-CH_2-N $(CH_2)_2$, also described in examples herein below.

[0073] Other preferred modifications include 2'-methoxy (2'-O CH_3), 2'-aminopropoxy (2'-O CH_2 CH_2 CH_2NH_2) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, each of which is herein incorporated by reference in its entirety.

[0074] Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylquanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine

and 3-deazaadenine. Further nucleobases include those disclosed in United States Patent No. 3,687,808, those disclosed in *The Concise Encyclopedia Of Polymer Science And Engineering*, pages 858-859, Kroschwitz, J.I., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y.S., Chapter 15, *Antisense Research and Applications*, pages 289-302, Crooke, S.T. and Lebleu, B. ed., CRC Press, 1993. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine, 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C (Sanghvi, Y.S., Crooke, S.T. and Lebleu, B., eds, *Antisense Research and Applications*, CRC Press, Boca Raton, 1993, pp. 276-278) and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

[0075] Representative United States patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. 3,687,808, as well as U.S.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,750,692, and 5,681,941, each of which is herein incorporated by reference.

[0076] Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates, which enhance the activity, cellular distribution, or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86, 6553-6556), cholic acid (Manoharan et al., *Bioorg. Med. Chem. Let.*, 1994, 4, 1053-1060), a

thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., *Ann. N.Y. Acad. Sci.*, 1992, 660, 306-309; Manoharan et al., *Bioorg. Med. Chem. Let.*, 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., *Nucl. Acids Res.*, 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., *EMBO J.*, 1991, 10, 1111-1118; Kabanov et al., *FEBS Lett.*, 1990, 259, 327-330; Svinarchuk et al., *Biochimie*, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 3651-3654; Shea et al., *Nucl. Acids Res.*, 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Mancharan et al., *Nucleosides & Nucleotides*, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., *Tetrahedron Lett.*, 1995, 36, 365'-3654), a palmityl moiety (Mishra et al., *Biochim. Biophys. Acta*, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., *J. Pharmacol. Exp. Ther.*, 1996, 277, 923-937).

[0077] Representative United States patents that teach the preparation of such oligonucleotide conjugates include, but are not limited to, U.S. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

[0078] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also

includes antisense compounds, which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease, which cleaves the RNA strand of RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxy oligonucleotides hybridizing to the same target region. Cleavage of the RNA target can be routinely detected by gel electrophoresis and, if necessary, associated nucleic acid hybridization techniques known in the art.

[0079] Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Such compounds have also been referred to in the art as hybrids or gapmers. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

[0080] The antisense compounds used in accordance with this invention may be conveniently, and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, CA). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives.

[0081] The antisense compounds of the invention are synthesized in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The compounds of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption assisting formulations include, but are not limited to, U.S. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

[0082] The antisense compounds of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such prodrugs, and other bioequivalents.

[0083] The term "prodrug" indicates a therapeutic agent that is prepared in an inactive form that is converted to an active form (i.e., drug) within the body or cells thereof by the action of endogenous enzymes or other chemicals and/or conditions. In particular, prodrug versions of the oligonucleotides of the invention are prepared as SATE [(S-acetyl-2-thioethyl) phosphate] derivatives according to the methods disclosed in WO 93/24510 to Gosselin et al., published December 9, 1993 or in WO 94/26764 to Imbach et al.

[0084] The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

[0085] Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N, N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., "Pharmaceutical Salts," *J. of Pharma Sci.*, 1977, 66, 119). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention. As used herein, a "pharmaceutical addition salt" includes a pharmaceutically acceptable salt of an acid form of one of the components of the compositions of the invention. These include organic or inorganic acid salts of the amines. Preferred acid salts are the hydrochlorides, acetates,

salicylates, nitrates, and phosphates. Other suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of a variety of inorganic and organic acids, such as, for example, with inorganic acids, such as for example hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid; with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, lactic acid, oxalic acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid; and with amino acids, such as the 20 alpha-amino acids involved in the synthesis of proteins in nature, for example glutamic acid or aspartic acid, and also with phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfoic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, N-cyclohexylsulfamic acid (with the formation of cyclamates), or with other acid organic compounds, such as ascorbic acid. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible.

[0086] For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid,

oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine.

[0087] The antisense compounds of the present invention can be utilized for diagnostics, therapeutics, prophylaxis, as research reagents, and kits. For therapeutics, an animal, preferably a human, suspected of having a disease or disorder, which can be treated by modulating the expression of ESM-1, is treated by administering antisense compounds in accordance with this invention. The compounds of the invention can be utilized in pharmaceutical compositions by adding an effective amount of an antisense compound to a suitable pharmaceutically acceptable diluent or carrier. Use of the antisense compounds and methods of the invention may also be useful prophylactically, e.g., to prevent or delay infection, inflammation, or tumor formation, for example.

[0088] The antisense compounds of the invention are useful for research and diagnostics, because these compounds hybridize to nucleic acids encoding ESM-1, enabling sandwich and other assays to easily be constructed to exploit this fact. Hybridization of the antisense oligonucleotides of the invention with a nucleic acid encoding ESM-1 can be detected by means known in the art. Such means may include conjugation of an enzyme to the oligonucleotide, radiolabelling of the oligonucleotide or any other suitable detection means. Kits using such detection means for detecting the level of ESM-1 in a sample may also be prepared.

[0089] The present invention also includes pharmaceutical compositions and formulations, which include the antisense compounds of the invention. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon

whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including vaginal and rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

[0090] Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids, and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves, and the like may also be useful.

[0091] Compositions and formulations for oral administration include powders or granules, suspensions, or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavoring agents, diluents, emulsifiers, dispersing aids, or binders may be desirable.

[0092] Compositions and formulations for parenteral, intrathecal or intraventricular administration may include sterile aqueous solutions, which may also contain buffers, diluents and other suitable additives such as, but not limited to, penetration enhancers, carrier compounds and other pharmaceutically acceptable carriers or excipients.

[0093] Pharmaceutical compositions of the present invention include, but are not limited to, solutions, emulsions, and liposome-containing formulations. These compositions may be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids.

[0094] The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be

prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0095] The compositions of the present invention may be formulated into any of many possible dosage forms such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas. The compositions of the present invention may also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions may further contain substances, which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol, and/or dextran. The suspension may also contain stabilizers.

[0096] In one embodiment of the present invention the pharmaceutical compositions may be formulated and used as foams. Pharmaceutical foams include formulations such as, but not limited to, emulsions, microemulsions, creams, jellies, and liposomes. While basically similar in nature these formulations vary in the components and the consistency of the final product. The preparation of such compositions and formulations is generally known to those skilled in the pharmaceutical and formulation arts and may be applied to the formulation of the compositions of the present invention. Emulsions

[0097] The compositions of the present invention may be prepared and formulated as emulsions. Emulsions are typically heterogenous systems of one liquid dispersed in another in the form of droplets usually exceeding 0.1 μm in diameter. (Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199; Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., Volume 1, p. 245; Block in

Pharmaceutical Dosage Forms, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 2, p. 335; Higuchi et al., in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 1985, p. 301). Emulsions are often biphasic systems comprising of two immiscible liquid phases intimately mixed and dispersed with each other. In general, emulsions may be either water-in-oil (w/o) or of the oil-in-water (o/w) variety. When an aqueous phase is finely divided into and dispersed as minute droplets into a bulk oily phase the resulting composition is called a water-in-oil (w/o) emulsion. Alternatively, when an oily phase is finely divided into and dispersed as minute droplets into a bulk aqueous phase the resulting composition is called an oil-in-water (o/w) emulsion. Emulsions may contain additional components in addition to the dispersed phases and the active drug, which may be present as a solution in either the aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants may also be present in emulsions as needed. Pharmaceutical emulsions may also be multiple emulsions that are comprised of more than two phases such as, for example, in the case of oil-in-water-in-oil (o/w/o) and water-in-oil-in-water (w/o/w) emulsions. Such complex formulations often provide certain advantages that simple binary emulsions do not. Multiple emulsions in which individual oil droplets of an o/w emulsion enclose small water droplets constitute a w/o/w emulsion. Likewise a system of oil droplets enclosed in globules of water stabilized in an oily continuous provides an o/w/o emulsion.

[0098] Emulsions are characterized by little or no thermodynamic stability. Often, the dispersed or discontinuous phase of the emulsion is well dispersed into the external or continuous phase and maintained in this form through the means of emulsifiers or the viscosity of the formulation. Either of the phases of the emulsion may be a semisolid or a solid, as is the case of emulsion-style ointment bases and creams. Other means of stabilizing emulsions entail the use of emulsifiers that may be incorporated into either phase of the emulsion. Emulsifiers may

broadly be classified into four categories: synthetic surfactants, naturally occurring emulsifiers, absorption bases, and finely dispersed solids (Idson, in *Pharmaceutical Dosaqe Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

[0099] Synthetic surfactants, also known as surface active agents, have found wide applicability in the formulation of emulsions and have been reviewed in the literature (Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), Marcel Dekker, Inc., New York, N.Y., 1988, volume 1, p. 199). Surfactants are typically amphiphilic and comprise a hydrophilic and a hydrophobic portion. The ratio of the hydrophilic to the hydrophobic nature of the surfactant has been termed the hydrophile/lipophile balance (HLB) and is a valuable tool in categorizing and selecting surfactants in the preparation of formulations. Surfactants may be classified into different classes based on the nature of the hydrophilic group: nonionic, anionic, cationic, and amphoteric (Rieger, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 285).

[00100] Naturally occurring emulsifiers used in emulsion formulations include lanolin, beeswax, phosphatides, lecithin, and acacia. Absorption bases possess hydrophilic properties such that they can soak up water to form w/o emulsions yet retain their semisolid consistencies, such as anhydrous lanolin and hydrophilic petrolatum. Finely divided solids have also been used as good emulsifiers especially in combination with surfactants and in viscous preparations. These include polar inorganic solids, such as heavy metal hydroxides, non-swelling clays such as bentonite, attapulgite, hectorite, kaolin, montmorillonite, colloidal aluminum silicate and colloidal magnesium aluminum silicate, pigments and nonpolar solids such as carbon or glyceryl tristearate.

[00101] A large variety of non-emulsifying materials are also included in emulsion formulations and contribute to the properties of emulsions. These include fats, oils, waxes, fatty acids, fatty alcohols, fatty esters, humectants, hydrophilic colloids, preservatives, and antioxidants (Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199).

[00102] Hydrophilic colloids or hydrocolloids include naturally occurring gums and synthetic polymers such as polysaccharides (for example, acacia, agar, alginic acid, carrageenan, guar gum, karaya gum, and tragacanth), cellulose derivatives (for example, carboxymethylcellulose and carboxypropylcellulose), and synthetic polymers (for example, carbomers, cellulose ethers, and carboxyvinyl polymers). These disperse or swell in water to form colloidal solutions that stabilize emulsions by forming strong interfacial films around the dispersed phase droplets and by increasing the viscosity of the external phase.

[00103] Since emulsions often contain a number of ingredients such as carbohydrates, proteins, sterols, and phosphatides that may readily support the growth of microbes, these formulations often incorporate preservatives. Commonly used preservatives included in emulsion formulations include methyl paraben, propyl paraben, quaternary ammonium salts, benzalkonium chloride, esters of p-hydroxybenzoic acid, and boric acid. Antioxidants are also commonly added to emulsion formulations to prevent deterioration of the formulation. Antioxidants used may be free radical scavengers such as tocopherols, alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, or reducing agents such as ascorbic acid and sodium metabisulfite, and antioxidant synergists such as citric acid, tartaric acid, and lecithin.

[00104] The application of emulsion formulations via dermatological, oral, and parenteral routes and methods for their manufacture have been

reviewed in the literature (Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Emulsion formulations for oral delivery have been very widely used because of reasons of ease of formulation, efficacy from an absorption and bioavailability standpoint. (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Idson, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 199). Mineral-oil base laxatives, oil-soluble vitamins, and high fat nutritive preparations are among the materials that have commonly been administered orally as o/w emulsions.

[00105] In one embodiment of the present invention, the compositions of oligonucleotides and nucleic acids are formulated as microemulsions. A microemulsion may be defined as a system of water, oil, and amphiphile, which is a single optically isotropic, and thermodynamically stable liquid solution (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245). Typically microemulsions are systems that are prepared by first dispersing an oil in an aqueous surfactant solution and then adding a sufficient amount of a fourth component, generally an intermediate chain-length alcohol to form a transparent system. Therefore, microemulsions have also been described as thermodynamically stable, isotropically clear dispersions of two immiscible liquids that are stabilized by interfacial films of surface-active molecules (Leung and Shah, in: *Controlled Release of Drugs: Polymers and Aggregate Systems*, Rosoff, M., Ed., 1989, VCH Publishers, New York, pages 1852-5). Microemulsions commonly are prepared via a combination of three to five components that include oil, water, surfactant, cosurfactant, and electrolyte. Whether the microemulsion is of the water-in-oil (w/o) or an oil-in-water (o/w) type is dependent on the properties of the oil and surfactant used and on the structure and geometric packing of the polar heads and hydrocarbon tails

of the surfactant molecules (Schott, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 1985, p. 271).

[00106] The phenomenological approach utilizing phase diagrams has been extensively studied and has yielded a comprehensive knowledge, to one skilled in the art, of how to formulate microemulsions (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 245; Block, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, p. 335). Compared to conventional emulsions, microemulsions offer the advantage of solubilizing water-insoluble drugs in a formulation of thermodynamically stable droplets that are formed spontaneously.

[00107] Surfactants used in the preparation of microemulsions include, but are not limited to, ionic surfactants, non-ionic surfactants, Brij 96, polyoxyethylene oleyl ethers, polyglycerol fatty acid esters, tetraglycerol monolaurate (ML310), tetraglycerol monooleate (MO310), hexaglycerol monooleate (PO310), hexaglycerol pentaoleate (PO500), decaglycerol monocaprate (MCA750), decaglycerol monooleate (MO750), decaglycerol sequioleate (S0750), decaglycerol decaoleate (DAO750), alone or in combination with cosurfactants. The cosurfactant, usually a short-chain alcohol such as ethanol, 1-propanol, and 1-butanol, serves to increase the interfacial fluidity by penetrating into the surfactant film and consequently creating a disordered film because of the void space generated among surfactant molecules. Microemulsions may, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase may typically be, but is not limited to, water, an aqueous solution of the drug, glycerol, PEG300, PEG400, polyglycerols, propylene glycols, and derivatives of ethylene glycol. The oil phase may include, but is not limited to, materials such as Captex 300, Captex 355, Capmul MCM, fatty acid esters, medium chain (C8-C12) mono, di, and triglycerides, polyoxyethylated glyceryl fatty

acid esters, fatty alcohols, polyglycolized glycerides, saturated polyglycolized C8-C10 glycerides, vegetable oils and silicone oil.

[00108] Microemulsions are particularly of interest from the standpoint of drug solubilization and the enhanced absorption of drugs. Lipid based microemulsions (both o/w and w/o) have been proposed to enhance the oral bioavailability of drugs, including peptides (Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385-1390; Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1993, 13, 205). Microemulsions afford advantages of improved drug solubilization, protection of drug from enzymatic hydrolysis, possible enhancement of drug absorption due to surfactant-induced alterations in membrane fluidity and permeability, ease of preparation, ease of oral administration over solid dosage forms, improved clinical potency, and decreased toxicity (Constantinides et al., *Pharmaceutical Research*, 1994, 11, 1385; Ho et al., *J. Pharm. Sci.*, 1996, 85, 138-143). Often microemulsions may form spontaneously when their components are brought together at ambient temperature. This may be particularly advantageous when formulating thermolabile drugs, peptides, or oligonucleotides. Microemulsions have also been effective in the transdermal delivery of active components in both cosmetic and pharmaceutical applications. It is expected that the microemulsion compositions and formulations of the present invention will facilitate the increased systemic absorption of oligonucleotides and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of oligonucleotides and nucleic acids within the gastrointestinal tract, vagina, buccal cavity and other areas of administration.

[00109] Microemulsions of the present invention may also contain additional components and additives such as sorbitan monostearate (Grill 3), Labrasol, and penetration enhancers to improve the properties of the formulation and to enhance the absorption of the oligonucleotides and nucleic acids of the present invention. Penetration enhancers used in the microemulsions of the present invention may be classified as belonging to one of five broad categories - surfactants, fatty acids, bile

salts, chelating agents, and non-chelating non-surfactants (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p. 92). Each of these classes has been discussed above.

[00110] Liposomes

[00111] There are many organized surfactant structures besides microemulsions that have been studied and used for the formulation of drugs. These include monolayers, micelles, bilayers, and vesicles. Vesicles, such as liposomes, have attracted great interest because of their specificity and the duration of action they offer from the standpoint of drug delivery. As used in the present invention, the term "liposome" means a vesicle composed of amphiphilic lipids arranged in a spherical bilayer or bilayers.

[00112] Liposomes are unilamellar or multilamellar vesicles which have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the composition to be delivered. Cationic liposomes possess the advantage of being able to fuse to the cell wall. Noncationic liposomes, although not able to fuse as efficiently with the cell wall, are taken up by macrophages in vivo.

[00113] In order to cross intact mammalian skin, lipid vesicles must pass through a series of fine pores, each with a diameter less than 50 nm, under the influence of a suitable transdermal gradient. Therefore, it is desirable to use a liposome, which is highly deformable and able to pass through such fine pores.

[00114] Further advantages of liposomes include; liposomes obtained from natural phospholipids are biocompatible and biodegradable; liposomes can incorporate a wide range of water and lipid soluble drugs; liposomes can protect encapsulated drugs in their internal compartments from metabolism and degradation (Rosoff, in *Pharmaceutical Dosage Forms*, Lieberman, Rieger and Banker (Eds.), 1988, Marcel Dekker, Inc., New York, N.Y., volume 1, P. 245). Important considerations in the preparation of liposome formulations are the lipid surface charge, vesicle size, and the aqueous volume of the liposomes.

[00115] Liposomes are useful for the transfer and delivery of active ingredients to the site of action. Because the liposomal membrane is structurally similar to biological membranes, when liposomes are applied to a tissue, the liposomes start to merge with the cellular membranes. As the merging of the liposome and cell progresses, the liposomal contents are emptied into the cell where the active agent may act.

[00116] Liposomal formulations have been the focus of extensive investigation as the mode of delivery for many drugs. There is growing evidence that for topical administration, liposomes present several advantages over other formulations. Such advantages include reduced side-effects related to high systemic absorption of the administered drug, increased accumulation of the administered drug at the desired target, and the ability to administer a wide variety of drugs, both hydrophilic and hydrophobic, into the skin.

[00117] Several reports have detailed the ability of liposomes to deliver agents including high-molecular weight DNA into the skin. Compounds including analgesics, antibodies, hormones, and high-molecular weight DNAs have been administered to the skin. The majority of applications resulted in the targeting of the upper epidermis.

[00118] Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes, which interact with the negatively charged DNA molecules to form a stable complex. The positively charged DNA/liposome complex binds to the negatively charged cell surface and is internalized in an endosome. Due to the acidic pH within the endosome, the liposomes are ruptured, releasing their contents into the cell cytoplasm (Wang et al., *Biochem. Biophys. Res. Commun.*, 1987, 147, 980 - 985)

[00119] Liposomes, which are pH-sensitive or negatively charged, entrap DNA rather than complex with it. Since both the DNA and the lipid are similarly charged, repulsion rather than complex formation occurs. Nevertheless, some DNA is entrapped within the aqueous interior of these liposomes. pH-sensitive liposomes have been used to

deliver DNA encoding the thymidine kinase gene to cell monolayers in culture. Expression of the exogenous gene was detected in the target cells (Zhou et al., *Journal of Controlled Release*, 1992, 19, 269-274).

[00120] One major type of liposomal composition includes phospholipids other than naturally derived phosphatidylcholine. Neutral liposome compositions, for example, can be formed from dimyristoyl phosphatidylcholine (DMPC) or dipalmitoyl phosphatidylcholine (DPPC). Anionic liposome compositions generally are formed from dimyristoyl phosphatidylglycerol, while anionic fusogenic liposomes are formed primarily from dioleoyl phosphatidylethanolamine (DOPE). Another type of liposomal composition is formed from phosphatidylcholine (PC) such as, for example, soybean PC, and egg PC. Another type is formed from mixtures of phospholipid and/or phosphatidylcholine and/or cholesterol.

[00121] Several studies have assessed the topical delivery of liposomal drug formulations to the skin. Application of liposomes containing interferon to guinea pig skin resulted in a reduction of skin herpes sores while delivery of interferon via other means (e.g. as a solution or as an emulsion) was ineffective (Weiner et al., *Journal of Drug Targeting*, 1992, 2, 405-410). Further, an additional study tested the efficacy of interferon administered as part of a liposomal formulation to the administration of interferon using an aqueous system, and concluded that the liposomal formulation was superior to aqueous administration (du Plessis et al., *Antiviral Research*, 1992, 18, 259-265).

[00122] Non-ionic liposomal systems have also been examined to determine their utility in the delivery of drugs to the skin, in particular systems comprising non-ionic surfactant and cholesterol. Non-ionic liposomal formulations comprising Novasome ™ I (glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl ether) and Novasome™ II (glyceryl distearate/ cholesterol/polyoxyethylene-10-stearyl ether) were used to deliver cyclosporin-A into the dermis of mouse skin. Results indicated that such non-ionic liposomal systems were effective

in facilitating the deposition of cyclosporin-A into different layers of the skin (Hu et al. *S.T.P.Pharma. Sci.*, 1994, 4, 6, 466).

[00123] Liposomes also include "sterically stabilized" liposomes, a term, which, as used herein, refers to liposomes comprising one or more specialized lipids that, when incorporated into liposomes, result in enhanced circulation lifetimes relative to liposomes lacking such, specialized lipids. Examples of sterically stabilized liposomes are those in which part of the vesicle-forming lipid portion of the liposome (A) comprises one or more glycolipids, such as monosialoganglioside G_{M1}, or (B) is derivatized with one or more hydrophilic polymers, such as a polyethylene glycol (PEG) moiety. While not wishing to be bound by any particular theory, it is thought in the art that, at least for sterically stabilized liposomes containing gangliosides, sphingomyelin, or PEG-derivatized lipids, the enhanced circulation half-life of these sterically stabilized liposomes derives from a reduced uptake into cells of the reticuloendothelial system (RES) (Allen et al., *FEBS Letters*, 1987, 223, 42; Wu et al., *Cancer Research*, 1993, 53, 3765).

[00124] Various liposomes comprising one or more glycolipids are known in the art. Papahadjopoulos et al. (*Ann. N.Y. Acad. Sci.*, 1987, 507, 64) reported the ability of monosialoganglioside G_{M1}, galactocerebroside sulfate, and phosphatidylinositol to improve blood half-lives of liposomes. These findings were expounded upon by Gabizon et al. (*Proc. Natl. Acad. Sci. U.S.A.*, 1988, 85, 6949). U.S. Patent No. 4,837,028 and WO 88/04924, both to Allen et al., disclose liposomes comprising (1) sphingomyelin and (2) the ganglioside Gjor a galactocerebroside sulfate ester. U.S. Patent No. 5,543,152 (Webb et al.) discloses liposomes comprising sphingomyelin. Liposomes comprising 1,2-sn-dimyristoylphosphatidylcholine are disclosed in WO 97/13499 (Lim et al.).

[00125] Many liposomes comprising lipids derivatized with one or more hydrophilic polymers, and methods of preparation thereof, are known in the art. Sunamoto et al. (*Bull. Chem. Soc. Jpn.*, 1980, 53, 2778) described liposomes comprising a nonionic detergent, $2C_{12}15G$,

which contains a PEG moiety. Illum et al. (*FEBS Lett.*, 1984, 167, 79) noted that hydrophilic coating of polystyrene particles with polymeric glycols results in significantly enhanced blood half-lives. Synthetic phospholipids modified by the attachment of carboxylic groups of polyalkylene glycols (e.g., PEG) are described by Sears (U.S. Patent Nos. 4,426,330 and 4,534,899). Klibanov et al. (*FEBS Lett.*, 1990, 268, 235) described experiments demonstrating that liposomes comprising phosphatidylethanolamine (PE) derivatized with PEG or PEG stearate have significant increases in blood circulation half-lives. Blume et al. (*Biochimica et Biophysica Acta*, 1990, 1029, 91) extended such observations to other PEG derivatized phospholipids, e.g., DSPE-PEG, formed from the combination of distearoylphosphatidylethanolamine (DSPE) and PEG. Liposomes having covalently bound PEG moieties on their external surface are described in European Patent No. EP 0 445 131 B1 and WO 90/04384 to Fisher. Liposome compositions containing 1-20 mole percent of PE derivatized with PEG, and methods of use thereof, are described by Woodle et al. (U.S. Patent Nos. 5,013,556 and 5,356,633) and Martin et al. (U.S. Patent No. 5,213,804 and European Patent No. EP 0 496 813 Bl). Liposomes comprising a number of other lipid-polymer conjugates are disclosed in WO 91/05545 and U.S. Patent No. 5,225,212 (both to Martin et al.) and in WO 94/20073 (Zalipsky et al.) Liposomes comprising PEG-modified ceramide lipids are described in WO 96/10391 (Choi et al.). U.S. Patent Nos. 5,540,935 (Miyazaki et al.) and 5,556,948 (Tagawa et al.) describe PEG-containing liposomes that can be further derivatized with functional moieties on their surfaces.

[00126] A limited number of liposomes comprising nucleic acids are known in the art. WO 96/40062 to Thierry et al. discloses methods for encapsulating high molecular weight nucleic acids in liposomes. U.S. Patent No. 5,264,221 to Tagawa et al. discloses protein-bonded liposomes and asserts that the contents of such liposomes may include an antisense RNA. U.S. Patent No. 5,665,710 to Rahman et al. describes certain methods of encapsulating oligodeoxynucleotides in liposomes.

WO 97/04787 to Love et al. discloses liposomes comprising antisense oligonucleotides targeted to the raf gene.

[00127] Transfersomes are yet another type of liposomes, and are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes may be described as lipid droplets, which are so highly deformable that they are easily able to penetrate through pores that are smaller than the droplet. Transfersomes are adaptable to the environment in which they are used, e.g. they are self-optimizing (adaptive to the shape of pores in the skin), self-repairing, frequently reach their targets without fragmenting, and often self-loading. To make transfersomes it is possible to add surface edge-activators, usually surfactants, to a standard liposomal composition. Transfersomes have been used to deliver serum albumin to the skin. The transfersome-mediated delivery of serum albumin has been shown to be as effective as subcutaneous injection of a solution containing serum albumin.

[00128] Surfactants find wide application in formulations such as emulsions (including microemulsions) and liposomes. The most common way of classifying and ranking the properties of the many different types of surfactants, both natural and synthetic, is by the use of the hydrophile/lipophile balance (HLB). The nature of the hydrophilic group (also known as the "head") provides the most useful means for categorizing the different surfactants used in formulations (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, NY, 1988, p. 285)

[00129] If the surfactant molecule is not ionized, it is classified as a nonionic surfactant. Nonionic surfactants find wide application in pharmaceutical and cosmetic products and are usable over a wide range of pH values. In general their HLB values range from 2 to about 18 depending on their structure. Nonionic surfactants include nonionic esters such as ethylene glycol esters, propylene glycol esters, glyceryl esters, polyglyceryl esters, sorbitan esters, sucrose esters, and ethoxylated esters. Nonionic alkanolamides and ethers such as fatty

alcohol ethoxylates, propoxylated alcohols, and ethoxylated/propoxylated block polymers are also included in this class. The polyoxyethylene surfactants are the most popular members of the nonionic surfactant class.

[00130] If the surfactant molecule carries a negative charge when it is dissolved or dispersed in water, the surfactant is classified as anionic. Anionic surfactants include carboxylates such as soaps, acyl lactylates, acyl amides of amino acids, esters of sulfuric acid such as alkyl sulfates and ethoxylated alkyl sulfates, sulfonates such as alkyl benzene sulfonates, acyl isethionates, acyl taurates and sulfosuccinates, and phosphates. The most important members of the anionic surfactant class are the alkyl sulfates and the soaps.

[00131] If the surfactant molecule carries a positive charge when it is dissolved or dispersed in water, the surfactant is classified as cationic. Cationic surfactants include quaternary ammonium salts and ethoxylated amines. The quaternary ammonium salts are the most used members of this class.

[00132] If the surfactant molecule has the ability to carry either a positive or negative charge, the surfactant is classified as amphoteric. Amphoteric surfactants include acrylic acid derivatives, substituted alkylamides, N-alkylbetaines, and phosphatides.

[00133] The use of surfactants in drug products, formulations and in emulsions has been reviewed (Rieger, in *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc., New York, NY, 1988, p. 285). Penetration Enhancers

[00134] In one embodiment, the present invention employs various penetration enhancers to effect the efficient delivery of nucleic acids particularly oligonucleotides, to the skin of animals. Most drugs are present in solution in both ionized and nonionized forms. However, usually only lipid soluble or lipophilic drugs readily cross cell membranes. It has been discovered that even non-lipophilic drugs may cross cell membranes if the membrane to be crossed is treated with a penetration enhancer. In addition to aiding the diffusion of non-

lipophilic drugs across cell membranes, penetration enhancers also enhance the permeability of lipophilic drugs.

[00135] Penetration enhancers may be classified as belonging to one of five broad categories, i.e., surfactants, fatty acids, bile salts, chelating agents, and non-chelating nonsurfactants (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92). Each of the above mentioned classes of penetration enhancers are described below in greater detail.

[00136] Surfactants: In connection with the present invention, surfactants (or "surface-active agents") are chemical entities which, when dissolved in an aqueous solution, reduce the surface tension of the solution or the interfacial tension between the aqueous solution and another liquid, with the result that absorption of oligonucleotides through the mucosa is enhanced. In addition to bile salts and fatty acids, these penetration enhancers include, for example, sodium lauryl sulfate, polyoxyethylene-9-lauryl ether and polyoxyethylene-20-cetyl ether) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92); and perfluorochemical emulsions, such as FC-43. Takahashi et al., *J. Pharm. Pharmacol.*, 1988, 40, 252).

[00137] Fatty acids: Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid (n-decanoic acid), myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, monoolein (1-monooleoyl-.rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glycerol 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, C_{1-10} alkyl esters thereof (e.g., methyl, isopropyl and t-butyl), and mono- and di-glycerides thereof (i.e., oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, etc.) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, p.92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; El Hariri et al., *J. Pharm. Pharmacol.*, 1992, 44, 651-654).

[00138] Bile salts: The physiological role of bile includes the facilitation of dispersion and absorption of lipids and fat-soluble

vitamins (Brunton, Chapter 38 in: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 9th Ed., Hardman et al. Eds. McGraw-Hill, New York, 1996, pp. 934-935). Various natural bile salts, and their synthetic derivatives, act as penetration enhancers. Thus the term "bile salts" includes any of the naturally occurring components of bile as well as any of their synthetic derivatives. The bile salts of the invention include, for example, cholic acid (or its pharmaceutically acceptable sodium salt, sodium cholate), dehydrocholic acid (sodium dehydrocholate), deoxycholic acid (sodium deoxycholate), glucholic acid (sodium glucholate), glycholic acid (sodium glycocholate), glycodeoxycholic acid (sodium glycodeoxycholate), taurocholic acid (sodium taurocholate), taurodeoxycholic acid (sodium taurodeoxycholate), chenodeoxycholic acid (sodium chenodeoxycholate), ursodeoxycholic acid (UDCA), sodium tauro-24,25-dihydro-fusidate (STDHF), sodium glycodihydrofusidate and polyoxyethylene-9-lauryl ether (POE) (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Swinyard, Chapter 39 In: *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, PA, 1990, pages 782-783; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Yamamoto et al., *J. Pharm. Exp. Ther.*, 1992, 263, 25; Yamashita et al., *J. Pharm. Sci.*, 1990, 79, 579-583).

[00139] Chelating Agents: Chelating agents, as used in connection with the present invention, can be defined as compounds that remove metallic ions from solution by forming complexes therewith, with the result that absorption of oligonucleotides through the mucosa is enhanced. With regards to their use as penetration enhancers in the present invention, chelating agents have the added advantage of also serving as DNase inhibitors, as most characterized DNA nucleases require a divalent metal ion for catalysis and are thus inhibited by chelating agents (Jarrett, *J. Chromatogr.*, 1993, 618, 315-339). Chelating agents of the invention include but are not limited to disodium. ethylenediaminetetraacetate (EDTA), citric acid, salicylates

(e.g., sodium salicylate, 5-methoxysalicylate and homovanilate), N-acyl derivatives of collagen, laureth-9, and N-amino acyl derivatives of beta-diketones (enamines)(Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92; Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33; Buur et al., *J. Control Rel.*, 1990, 14, 43-51).

[00140] Non-chelating non-surfactants: As used herein, nonchelating non-surfactant penetration enhancing compounds can be defined as compounds that demonstrate insignificant activity as chelating agents or as surfactants but that nonetheless enhance absorption of oligonucleotides through the alimentary mucosa (Muranishi, *Critical Reviews in Therapeutic Drug Carrier Systems*, 1990, 7, 1-33). This class of penetration enhancers includes, for example, unsaturated cyclic ureas, 1-alkyl- and 1-alkenylazacyclo-alkanone derivatives (Lee et al., *Critical Reviews in Therapeutic Drug Carrier Systems*, 1991, page 92); and non-steroidal anti-inflammatory agents such as diclofenac sodium, indomethacin, and phenylbutazone (Yamashita et al., *J. Pharm. Pharmacol.*, 1987, 39, 621-626).

[00141] Agents that enhance uptake of oligonucleotides at the cellular level may also be added to the pharmaceutical and other compositions of the present invention. For example, cationic lipids, such as lipofectin (Junichi et al, U.S. Patent No. 5,705,188), cationic glycerol derivatives, and polycationic molecules, such as polylysine (Lollo et al., PCT Application WO 97/30731), are also known to enhance the cellular uptake of oligonucleotides.

[00142] Other agents may be utilized to enhance the penetration of the administered nucleic acids, including glycols such as ethylene glycol and propylene glycol, pyrrols such as 2-pyrrol, azones, and terpenes such as limonene and menthone.

Carriers

[00143] Certain compositions of the present invention also incorporate carrier compounds in the formulation. As used herein, "carrier compound" or "carrier" can refer to a nucleic acid, or analog

thereof, which is inert (i.e., does not possess biological activity per se) but is recognized as a nucleic acid by in vivo processes that reduce the bioavailability of a nucleic acid having biological activity by, for example, degrading the biologically active nucleic acid or promoting its removal from circulation. The coadministration of a nucleic acid and a carrier compound, typically with an excess of the latter substance, can result in a substantial reduction of the amount of nucleic acid recovered in the liver, kidney or other extracirculatory reservoirs, presumably due to competition between the carrier compound and the nucleic acid for a common receptor. For example, the recovery of a partially phosphorothioate oligonucleotide in hepatic tissue can be reduced when it is coadministered with polyinosinic acid, dextran sulfate, polycytidic acid or 4-acetamido-4'isothiocyano-stilbene-2,2'disulfonic acid (Miyao et al., *Antisense Res. Dev.*, 1995, 5, 115-121; Takakura et al., *Antisense & Nucl. Acid Drug Dev.*, 1996, 6, 177-183).

Excipients

[00144] In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient may be liquid or solid and is selected, with the planned manner of administration in mind, so as to provide for the desired bulk, consistency, etc., when combined with a nucleic acid and the other components of a given pharmaceutical composition. Typical pharmaceutical carriers include, but are not limited to, binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose, etc.); fillers (e.g., lactose and other sugars, microcrystalline cellulose, pectin, gelatin, calcium sulfate, ethyl cellulose, polyacrylates or calcium hydrogen phosphate, etc.); lubricants (e.g., magnesium stearate, talc, silica, colloidal silicon dioxide, stearic acid, metallic stearates, hydrogenated vegetable oils, corn starch, polyethylene glycols, sodium benzoate, sodium acetate, etc.); disintegrants (e.g., starch, sodium starch glycolate, etc.); and wetting agents (e.g., sodium lauryl sulphate, etc.).

[00145] Pharmaceutically acceptable organic or inorganic excipient suitable for non-parenteral administration, which does not deleteriously react with nucleic acids, can also be used to formulate the compositions of the present invention. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

[00146] Formulations for topical administration of nucleic acids may include sterile and non-sterile aqueous solutions, non-aqueous solutions in common solvents such as alcohols, or solutions of the nucleic acids in liquid or solid oil bases. The solutions may also contain buffers, diluents, and other suitable additives. Pharmaceutically acceptable organic or inorganic excipients suitable for non-parenteral administration, which do not deleteriously react with nucleic acids, can be used.

[00147] Suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose, polyvinylpyrrolidone and the like.

Other Components

[00148] The compositions of the present invention may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized

and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

[00149] Aqueous suspensions may contain substances, which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol, and/or dextran. The suspension may also contain stabilizers.

[00150] Certain embodiments of the invention provide pharmaceutical compositions containing (a) one or more antisense compounds and (b) one or more other chemotherapeutic agents which function by a non-antisense mechanism. Examples of such chemotherapeutic agents include, but are not limited to, anticancer drugs such as daunorubicin, dactinomycin, doxorubicin, bleomycin, mitomycin, nitrogen mustard, chlorambucil, melphalan, cyclophosphamide, 6-mercaptopurine, 6-thioguanine, cytarabine (CA), 5-fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate (MTX), colchicine, vincristine, vinblastine, etoposide, teniposide, cisplatin and diethylstilbestrol (DES). See, generally, *The Merck Manual of Diagnosis and Therapy*, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 1206-1228). Anti-inflammatory drugs, including but not limited to nonsteroidal anti-inflammatory drugs and corticosteroids, and antiviral drugs, including but not limited to ribivirin, vidarabine, acyclovir and ganciclovir, may also be combined in compositions of the invention. See, generally, *The Merck Manual of Diagnosis and Therapy*, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J., pages 2499-2506 and 46-49, respectively). other non-antisense chemotherapeutic agents are also within the scope of this invention. Two or more combined compounds may be used together or sequentially.

[00151] In another related embodiment, compositions of the invention may contain one or more antisense compounds, particularly oligonucleotides, targeted to a first nucleic acid and one or more

additional antisense compounds targeted to a second nucleic acid target. Numerous examples of antisense compounds are known in the art. Two or more combined compounds may be used together or sequentially.

[00152] The formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50}s found to be effective in in vitro and in vivo animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein the oligonucleotide is administered in maintenance doses, ranging from 0.01 μg to 100 g per kg of body weight, once or more daily, to once every 20 years.

[00153] While the present invention has been described with specificity in accordance with certain of its preferred embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same.

EXAMPLES

Example 1

Nucleoside Phosphoramidites for Oligonucleotide Synthesis Deoxy and 2'-alkoxy amidites

[00154] 2'-Deoxy and 2'-methoxy beta-cyanoethyldiisopropyl phosphoramidites are available from commercial sources (e.g. Chemgenes, Needham MA or Glen Research, Inc. Sterling VA). Other 2'-O-alkoxy substituted nucleoside amidites are prepared as described in U.S. Patent 5,506,351, herein incorporated by reference. For oligonucleotides synthesized using 2'-alkoxy amidites, the standard cycle for unmodified oligonucleotides is utilized, except the wait step after pulse delivery of tetrazole and base is increased to 360 seconds.

[00155] Oligonucleotides containing 5-methyl-2'-deoxycytidine (5-Me-C) nucleotides are synthesized according to published methods [Sanghvi, et. al., *Nucleic Acids Research*, 1993, 21, 3197-3203] using commercially available phosphoramidites (Glen Research, Sterling VA or ChemGenes, Needham MA).

2'-Fluoro amidites

2'-Fluorodeoxyadenosine amidites

[00156] 2'-fluoro oligonucleotides are synthesized as described previously [Kawasaki, et. al., *J. Med. Chem.*, 1993, 36, 831-841] and United States patent 5,670,633, herein incorporated by reference. Briefly, the protected nucleoside N6-benzoyl-2'-deoxy-2'-fluoroadenosine is synthesized utilizing commercially available 9-beta-D-arabinofuranosyladenine as starting material and by modifying literature procedures whereby the 2'-alpha-fluoro atom is introduced by a S_N2-displacement of a 2'-beta-trityl group. Thus N6-benzoyl-9-beta-D-arabinofuranosyladenine is selectively protected in moderate yield as the 3',5'-ditetrahydropyranyl (THP) intermediate. Deprotection of the THP and N6-benzoyl groups is accomplished using standard methodologies and standard methods are used to obtain the 5'-dimethoxytrityl-(DMT) and 5'-DMT-3'-phosphoramidite intermediates.

2'-Fluorodeoxyguanosine

[00157] The synthesis of 2'-deoxy-2'-fluoroguanosine is accomplished using tetraisopropyldisiloxanyl (TPDS) protected 9-beta-D-arabinofuranosylguanine as starting material, and conversion to the intermediate diisobutyrylarabinofuranosylguanosine. Deprotection of the

TPDS group is followed by protection of the hydroxyl group with THP to give diisobutyryl di-THP protected arabinofuranosylguanine. Selective O-deacylation and triflation is followed by treatment of the crude product with fluoride, then deprotection of the THP groups. Standard methodologies are used to obtain the 5'-DMT- and 5'-DMT-3'-phosphoramidites.

2'-Fluorouridine

[00158] Synthesis of 2'-deoxy-2'-fluorouridine is accomplished by the modification of a literature procedure in which 2,2'anhydro-l-beta-D-arabinofuranosyluracil is treated with 70% hydrogen fluoride-pyridine. Standard procedures are used to obtain the 5'-DMT and 5'-DMT-3'-phosphoramidites.

2'-Fluorodeoxycytidine

[00159] 2'-deoxy-2'-fluorocytidine is synthesized via amination of 2'-deoxy-2'-fluorouridine, followed by selective protection to give N4-benzoyl-2'-deoxy-2'-fluorocytidine. Standard procedures are used to obtain the 5'-DMT and 5'-DMT-3'phosphoramidites.

2'-O-(2-Methoxyethyl) modified amidites

[00160] 2'-O-Methoxyethyl-substituted nucleoside amidites are prepared as follows, or alternatively, as per the methods of Martin, P., *Helvetica Chimica Acta*, 1995, 78, 486-504.

2,2'-Anhydro[l-(beta-D-arabinofuranosyl)-5-methyluridinel

[00161] 5-Methyluridine (ribosylthymine, commercially available through Yamasa, Choshi, Japan) (72.0 g, 0.279 M), diphenylcarbonate (90.0 g, 0.420 M) and sodium bicarbonate (2.0 g, 0.024 M) are added to DMF (300 mL). The mixture is heated to reflux, with stirring, allowing the evolved carbon dioxide gas to be released in a controlled manner. After 1 hour, the slightly darkened solution is concentrated under reduced pressure. The resulting syrup is poured into diethylether (2.5 L), with stirring. The product formed a gum. The ether is decanted and the residue is dissolved in a minimum amount of methanol (ca. 400 mL). The solution is poured into fresh ether (2.5 L) to yield a stiff gum. The ether is decanted and the gum is dried in a vacuum oven (60°C at 1 mm

Hg for 24 h) to give a solid that is crushed to a light tan powder. The material is used as is for further reactions (or it can be purified further by column chromatography using a gradient of methanol in ethyl acetate (10-25%) to give a white solid.

2'-O-Methoxyethyl-5-methyluridine

[00162] 2,2'-Anhydro-5-methyluridine (195 g, 0.81 M), tris(2-methoxyethyl)borate (231 g, 0.98 M) and 2-methoxyethanol (1.2 L) are added to a 2 L stainless steel pressure vessel and placed in a pre-heated oil bath at 160°C. After heating for 48 hours at 155-160°C, the vessel is opened and the solution evaporated to dryness and triturated with MeOH (200 mL). The residue is suspended in hot acetone (1 L). The insoluble salts are filtered, washed with acetone (150 mL) and the filtrate evaporated. The residue (280 g) is dissolved in CH_3CN (600 mL) and evaporated. A silica gel column (3 kg) is packed in CH_2Cl_2 /acetone /MeOH (20:5:3) containing 0.5% Et_3NH. The residue is dissolved in CH_2Cl_2 (250 mL) and adsorbed onto silica (150 g) prior to loading onto the column. The product is eluted with the packing solvent to give the title product. Additional material can be obtained by reworking impure fractions.

2'-O-Methoxyethyl-5'-O-dimethoxytrityl-5-methyluridine

[00163] 2'-O-Methoxyethyl-5-methyluridine (160 g, 0.506 M) is co-evaporated with pyridine (250 mL) and the dried residue dissolved in pyridine (1.3 L). A first aliquot of dimethoxytrityl chloride (94.3 g, 0.278 M) is added and the mixture stirred at room temperature for one hour. A second aliquot of dimethoxytrityl chloride (94.3 g, 0.278 M) is added and the reaction stirred for an additional one hour. Methanol (170 mL) is then added to stop the reaction. The solvent is evaporated and triturated with CH_3CN (200 mL) The residue is dissolved in CHCl (1.5 L) and extracted with 2x500 mL of saturated $NaHCO_3$ and 2x500 mL of saturated NaCl. The organic phase is dried over Na_2SO_4, filtered, and evaporated. The residue is purified on a 3.5 kg silica gel column, packed and eluted with EtOAc/hexane/ acetone (5:5:1) containing 0-5% Et_3NH. The pure fractions are evaporated to give the title product.

3'-O-Acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyluridine

[00164] 2'-O-Methoxyethyl-5'-O-dimethoxytrityl-5-methyluridine (106 g, 0.167 M), DMF/pyridine (750 mL of a 3:1 mixture prepared from 562 mL of DMF and 188 mL of pyridine) and acetic anhydride (24.38 mL, 0.258 M) are combined and stirred at room temperature for 24 hours. The reaction is monitored by TLC by first quenching the TLC sample with the addition of MeOH. Upon completion of the reaction, as judged by TLC, MeOH (50 mL) is added and the mixture evaporated at 35°C. The residue is dissolved in $CHCl_3$ (800 mL) and extracted with 2x200 mL of saturated sodium bicarbonate and 2x200 mL of saturated NaCl. The water layers are back extracted with 200 mL of $CHCl_3$. The combined organics are dried with sodium sulfate and evaporated to a residue. The residue is purified on a 3.5 kg silica gel column and eluted using EtOAc/hexane(4:1). Pure product fractions are evaporated to yield the title compounds.

3'-O-Acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyl-4-triazoleuridine

[00165] A first solution is prepared by dissolving 3'-O-acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyluridine (96 g, 0.144 M) in CH_3CN (700 mL) and set aside. Triethylamine (189 mL, 1.44 M) is added to a solution of triazole (90 g, 1.3 M) in CH_3CN (1 L), cooled to –5°C and stirred for 0.5 h using an overhead stirrer. $POCl_3$ is added dropwise, over a 30 minute period, to the stirred solution maintained at 0-10°C, and the resulting mixture stirred for an additional 2 hours. The first solution is added dropwise, over a 45 minute period, to the latter solution. The resulting reaction mixture is stored overnight in a cold room. Salts are filtered from the reaction mixture and the solution is evaporated. The residue is dissolved in EtOAc (1 L) and the insoluble solids are removed by filtration. The filtrate is washed with 1x300 mL of $NaHCO_3$ and 2x300 mL of saturated NaCl, dried over sodium sulfate and evaporated. The residue is triturated with EtOAc to give the title compound.

2'-O-Methoxyethyl-5'-O-dimethoxytrityl-5-methylcytidine

[00166] A solution of 3'-O-acetyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methyl-4-triazoleuridine (103 g, 0.141 M) in dioxane (500 mL) and NH_4OH (30 mL) is stirred at room temperature for 2 hours. The dioxane solution is evaporated and the residue azeotroped with MeOH (2x200 mL). The residue is dissolved in MeOH (300 mL) and transferred to a 2-liter stainless steel pressure vessel. MeOH (400 mL) saturated with NH_3 gas is added and the vessel heated to 100°C for 2 hours (TLC showed complete conversion). The vessel contents are evaporated to dryness and the residue is dissolved in EtOAc (500 mL) and washed once with saturated NaCl (200 mL). The organics are dried over sodium sulfate and the solvent is evaporated to give the title compound.

N4-Benzoyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methylcytidine

[00167] 2'-O-Methoxyethyl-5'-O-dimethoxytrityl-5-methylcytidine (85 g, 0.134 M) is dissolved in DMF (800 mL) and benzoic anhydride (37.2 g, 0.165 M) is added with stirring. After stirring for 3 hours, TLC showed the reaction to be approximately 95% complete. The solvent is evaporated and the residue azeotroped with MeOH (200 mL). The residue is dissolved in $CHCl_3$ (700 mL) and extracted with saturated NaHCO, (2x300 mL) and saturated NaCl (2x300 mL) , dried over $MgSO_4$ and evaporated to give a residue. The residue is chromatographed on a 1.5 kg silica column using EtOAc/hexane (1:1) containing 0-5% Et_3NH as the eluting solvent. The pure product fractions are evaporated to give the title compound.

N4-Benzoyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methylcytidine-3'-amidite

[00168] N4-Benzoyl-2'-O-methoxyethyl-5'-O-dimethoxytrityl-5-methylcytidine (74 g, 0.10 M) is dissolved in CH_2Cl_2 (1 L) Tetrazole diisopropylamine (7.1 g) and 2-cyanoethoxy-tetra(isopropyl)phosphite (40.5 mL, 0.123 M) are added with stirring, under a nitrogen atmosphere. The resulting mixture is stirred for 20 hours at room

temperature (TLC showed the reaction to be 95% complete). The reaction mixture is extracted with saturated $NaHCO_3$ (1x300 mL) and saturated NaCl (3x300 mL). The aqueous washes are back-extracted with CH_2Cl_2 (300 mL), and the extracts are combined, dried over $MgSO_4$, and concentrated. The residue obtained is chromatographed on a 1.5 kg silica column using EtOAc/hexane (3:1) as the eluting solvent. The pure fractions were combined to give the title compound.

2'-O-(Aminooxyethyl) nucleoside amidites and 2'-O-(dimethylaminooxyethyl) nucleoside amidites

2'-(Dimethylaminooxyethoxy) nucleoside amidites

[00169] 2'-(Dimethylaminooxyethoxy) nucleoside amidites [also known in the art as 2'-O-(dimethylaminooxyethyl) nucleoside amidites] are prepared as described in the following paragraphs. Adenosine, cytidine and guanosine nucleoside amidites are prepared similarly to the thymidine (5-methyluridine) except the exocyclic amines are protected with a benzoyl moiety in the case of adenosine and cytidine and with isobutyryl in the case of guanosine.

5'-O-tert-Butyldiphenylsilyl -O^2 -2'-anhydro-5-methyluridine

[00170] O^2 -2'-anhydro-5-methyluridine (Pro. Bio. Sint., Varese, Italy, 100.0g, 0.4'6 mmol), dimethylaminopyridine (0.66g, 0.013eq, 0.0054mmol) are dissolved in dry pyridine (500 ml) at ambient temperature under an argon atmosphere and with mechanical stirring. tert-Butyldiphenylchlorosilane (125.8g, 119.0mL, 1.1eq, 0.458mmol) is added in one portion. The reaction is stirred for 16 h at ambient temperature. TLC (Rf 0.22, ethyl acetate) indicated a complete reaction. The solution is concentrated under reduced pressure to a thick oil. This is partitioned between dichloromethane (1 L) and saturated sodium bicarbonate (2xl L) and brine (1 L). The organic layer is dried over sodium sulfate and concentrated under reduced pressure to a thick oil. The oil is dissolved in a 1:1 mixture of ethyl acetate and ethyl ether (600mL) and the solution is cooled to –10°C. The resulting crystalline product is collected by filtration, washed with ethyl ether (3x200 mL), and dried (40°C, 1mm Hg, 24 h) to a white solid

5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine

[00171] In a 2 L stainless steel, unstirred pressure reactor is added borane in tetrahydrofuran (1.0 M, 2.0 eq, 622 mL). In the fume hood and with manual stirring, ethylene glycol (350 mL, excess) is added cautiously at first until the evolution of hydrogen gas subsides. 5'-O-tert-Butyldiphenylsilyl-O^2-2'anhydro-5-methyluridine (149 g, 0.3'1 mol) and sodium bicarbonate (0.074 g, 0.003 eq) are added with manual stirring. The reactor is sealed and heated in an oil bath until an internal temperature of 160°C is reached and then maintained for 16 h (pressure < 100 psig). The reaction vessel is cooled to ambient and opened. TLC (Rf 0.67 for desired product and Rf 0.82 for ara-T side product, ethyl acetate) indicated about 70% conversion to the product. In order to avoid additional side product formation, the reaction is stopped, concentrated under reduced pressure (10 to 1mm, Hg) in a warm water bath (40-100°C) with the more extreme conditions used to remove the ethylene glycol. [Alternatively, once the low boiling solvent is gone, the remaining solution can be partitioned between ethyl acetate and water. The product will be in the organic phase.] The residue is purified by column chromatography (2kg silica gel, ethyl acetate-hexanes gradient 1:1 to 4:1). The appropriate fractions are combined, stripped, and dried to product as a white crisp foam, contaminated starting material, and pure reusable starting material.

2'-O-([2-phthalimidoxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine

[00172] 5'-O-tert-Butyldiphenylsilyl-2'-O-(2-hydroxyethyl)-5-methyluridine (20g, 36.98mmol) is mixed with triphenylphosphine (11.63g, 44.36mmol) and N-hydroxyphthalimide (7.24g, 44.36mmol). It is then dried over P_2O_5 under high vacuum for two days at 40°C. The reaction mixture is flushed with argon and dry THF (369.8mL, Aldrich, sure seal bottle) is added to get a clear solution. Diethyl-azodicarboxylate (6.98mL, 44.36mmol) is added dropwise to the reaction mixture. The rate of addition is maintained such that resulting deep red coloration is just discharged before adding the next drop. After

the addition is complete, the reaction is stirred for 4 hrs. By that time TLC showed the completion of the reaction (ethylacetate:hexane, 60:40). The solvent is evaporated in vacuum. Residue obtained is placed on a flash column and eluted with ethyl acetate:hexane (60:40), to get 2'-O-([2-phthalimidoxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine as white foam.

5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine

[00173] 2'-O-([2-phthalimidoxy)ethyl]-5'-t-butyldiphenylsilyl-5-methyluridine (3.1g, 4.5mmol) is dissolved in dry CH_2Cl_2 (4.5mL) and methylhydrazine (300mL, 4.64mmol) is added dropwise at −10°C to 0°C. After 1 h the mixture is filtered, the filtrate is washed with ice cold CH_2Cl_2 and the combined organic phase is washed with water, brine and dried over anhydrous Na_2SO_4. The solution is concentrated to get 2'-O(aminooxyethyl) thymidine, which is then dissolved in MeOH (67.5mL). To this formaldehyde (20% aqueous solution, w/w, 1.1 eq.) is added and the resulting mixture is stirred for 1 h. Solvent is removed under vacuum; residue chromatographed to get 5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy) ethyl]-5-methyluridine as white foam.

5'-O-tert-Butyldiphenylsilyl-2'-O-[N,N-dimethylaminooxyethyl]-5-methyluridine

[00174] 5'-O-tert-butyldiphenylsilyl-2'-O-[(2-formadoximinooxy)ethyl]-5-methyluridine (1.77g, 3.12mmol) is dissolved in a solution of 1M pyridinium p-toluenesulfonate (PPTS) in dry MeOH (30.6mL). Sodium cyanoborohydride (0.39g, 6.13mmol) is added to this solution at 10°C under inert atmosphere. The reaction mixture is stirred for 10 minutes at 10°C. After that the reaction vessel is removed from the ice bath and stirred at room temperature for 2 h, the reaction monitored by TLC (5% MeOH in CH_2Cl_2). Aqueous $NaHCO_3$ solution (5%, 10mL) is added and extracted with ethyl acetate (2x20mL). Ethyl acetate phase is dried over anhydrous Na_2SO_4, evaporated to dryness. Residue is dissolved in a solution of 1M PPTS in

MeOH (30.6mL). Formaldehyde (20% w/w, 30mL, 3.37mmol) is added and the reaction mixture is stirred at room temperature for 10 minutes. Reaction mixture cooled to 10°C in an ice bath, sodium cyanoborohydride (0.39g, 6.13mmol) is added, and reaction mixture stirred at 10°C for 10 minutes. After 10 minutes, the reaction mixture is removed from the ice bath and stirred at room temperature for 2 hrs. To the reaction mixture 5% $NaHCO_3$ (25mL) solution is added and extracted with ethyl acetate (2x25mL). Ethyl acetate layer is dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue obtained is purified by flash column chromatography and eluted with 5% MeOH in CH_2Cl_2 to get 5'-O-tertbutyldiphenylsilyl-2'-O-[N,N-dimethylaminooxyethyl]-5- methyluridine as a white foam.

2'-O-(dimethylaminooxyethyl)-5-methyluridine

[00175] Triethylamine trihydrofluoride (3.91mL, 24.0mmol) is dissolved in dry THF and triethylamine (1.67mL, 12mmol, dry, kept over KOH). This mixture of triethylamine-2HF is then added to 5'-O-tert-butyldiphenylsilyl-2'-O-[N,N-dimethylaminooxyethyl]-5-methyluridine (1.40g, 2.4mmol) and stirred at room temperature for 24 hrs. Reaction is monitored by TLC (5% MeOH in CH_2Cl_2). Solvent is removed under vacuum and the residue placed on a flash column and eluted with 10% MeOH in CH_2Cl_2 to get 2'-O-(dimethylaminooxyethyl)-5-methyluridine.

5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine

[00176] 2'-O-(dimethylaminooxyethyl)-5-methyluridine (750mg, 2.17mmol) is dried over P_2O_5 under high vacuum overnight at 40°C. It is then co-evaporated with anhydrous pyridine (20mL). The residue obtained is dissolved in pyridine (11mL) under argon atmosphere. 4-dimethylaminopyridine (26.5mg, 2.60mmol), 4,4'-dimethoxytrityl chloride (880mg, 2.60mmol) is added to the mixture and the reaction mixture is stirred at room temperature until all of the starting material disappeared. Pyridine is removed under vacuum and the residue chromatographed and eluted with 10% MeOH in CH_2Cl_2 (containing a

few drops of pyridine) to get 5'-O-DMT-2'-0(dimethylamino-oxyethyl)-5-methyluridine.

5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-N,N- diisopropylphosphoramidite]

[00177] 5'-O-DMT-2'-O-(dimethylaminooxyethyl)-5-methyluridine (1.08g, 1.67mmol) is co-evaporated with toluene (20mL). To the residue N,N-diisopropylamine tetrazonide (0.29g, 1.67mmol) is added and dried over P20, under high vacuum overnight at 40°C. Then the reaction mixture is dissolved in anhydrous acetonitrile (8.4mL) and 2-cyanoethyl-N,N,N^1,N^1-tetraisopropylphosphoramidite (2.12mL, 6.08mmol) is added. The reaction mixture is stirred at ambient temperature for 4 hrs under inert atmosphere. The progress of the reaction is monitored by TLC (hexane:ethyl acetate 1:1). The solvent is evaporated, then the residue is dissolved in ethyl acetate (70mL) and washed with 5% aqueous $NaHCO_3$ (40mL). Ethyl acetate layer is dried over anhydrous Na_2SO_4 and concentrated. Residue obtained is chromatographed (ethyl acetate as eluent) to get 5'-O-DMT-2'-O-(2-N,N-dimethylaminooxyethyl)-5-methyluridine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite] as a foam.

2'-(Aminooxyethoxy) nucleoside amidites

[00178] 2'-(Aminooxyethoxy) nucleoside amidites [also known in the art as 2'-O-(aminooxyethyl) nucleoside amidites] are prepared as described in the following paragraphs. Adenosine, cytidine and thymidine nucleoside amidites are prepared similarly.

N2-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramidite]

[00179] The 2'-O-aminooxyethyl guanosine analog may be obtained by selective 2'-O-alkylation of diaminopurine riboside. Multigram quantities of diaminopurine riboside may be purchased from Schering AG (Berlin) to provide 2'-O-(2-ethylacetyl) diaminopurine riboside along with a minor amount of the 3'-O-isomer. 2'-O-(2-ethylacetyl) diaminopurine riboside may be resolved and converted to 2'-O-

(2ethylacetyl)guanosine by treatment with adenosine deaminase. (McGee, D. P. C., Cook, P. D., Guinosso, C. J., WO 94/02501 Al 940203.) Standard protection procedures should afford 2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine and 2-N-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine which may be reduced to provide 2-N-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine. As before the hydroxyl group may be displaced by N-hydroxyphthalimide via a Mitsunobu reaction, and the protected nucleoside may phosphitylated as usual to yield 2-N-isobutyryl-6-O-diphenylcarbamoyl-2'-O-(2-ethylacetyl)-5'-O-(4,4'-dimethoxytrityl)guanosine-3'-[(2-cyanoethyl)-N,N-diisopropylphosphoramiditel.

2'-dimethylaminoethoxyethoxy (2'-DMAEOE) nucleoside amidites

[00180] 2'-dimethylaminoethoxyethoxy nucleoside amidites (also known in the art as 2'-O-dimethylaminoethoxyethyl, i.e., 2'O-CH_2-O-CH_2-N$(CH_2)_2$, or 2'-DMAEOE nucleoside amidites) are prepared as follows. Other nucleoside amidites are prepared similarly.

2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl]-5-methyl uridine

[00181] 2[2-(Dimethylamino)ethoxylethanol (Aldrich, 6.66 g, 50 mmol) is slowly added to a solution of borane in tetrahydrofuran (1 M, 10 mL, 10 mmol) with stirring in a 100 mL bomb. Hydrogen gas evolves as the solid dissolves. O^2-, 2' - anhydro-5-methyluridine (1.2 g, 5 mmol), and sodium bicarbonate (2.5 mg) are added and the bomb is sealed, placed in an oil bath, and heated to 155°C for 26 hours. The bomb is cooled to room temperature and opened. The crude solution is concentrated and the residue partitioned between water (200 mL) and hexanes (200 mL). The excess phenol is extracted into the hexane layer. The aqueous layer is extracted with ethyl acetate (3x200 mL) and the combined organic layers are washed once with water, dried over anhydrous sodium sulfate, and concentrated. The residue is columned on silica gel using methanol/methylene chloride 1:20 (which has 2% triethylamine) as the eluent. As the column fractions are concentrated a

colorless solid forms which is collected to give the title compound as a white solid.

5'-O-dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy) ethyl)]-5-methyl uridine

[00182] To 0.5 g (1.3 mmol) of 2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl)1-5-methyl uridine in anhydrous pyridine (8 mL), triethylamine (0.36 mL) and dimethoxytrityl chloride (DMT-Cl, 0.87 g, 2 eq.) are added and stirred for 1 hour. The reaction mixture is poured into water (200 mL) and extracted with CH_2Cl_2 (2x200 mL). The combined CH_2Cl_2 layers are washed with saturated $NaHCO_3$ solution, followed by saturated NaCl solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by silica gel chromatography using MeOH: CH_2Cl_2:Et_3N (20:1, v/v, with 1% triethylamine) gives the title compound.

5'-O-Dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl)]-5-methyl uridine-3'-O-(cyanoethyl-N,N-diisopropyl)phosphoramidite

[00183] Diisopropylaminotetrazolide (0.6 g) and 2-cyanoethoxyN,N-diisopropyl phosphoramidite (1.1 mL, 2 eq.) are added to a solution of 5'-O-dimethoxytrityl-2'-O-[2(2-N,N-dimethylaminoethoxy)ethyl)]-5-methyluridine (2.17 g, 3 mmol) dissolved in CH_2Cl_2 (20 mL) under an atmosphere of argon. The reaction mixture is stirred overnight and the solvent evaporated. The resulting residue is purified by silica gel flash column chromatography with ethyl acetate as the eluent to give the title compound.

Example 2

Oligonucleotide synthesis

[00184] Unsubstituted and substituted phosphodiester (P=O) oligonucleotides are synthesized on an automated DNA synthesizer (Applied Biosystems model 380B) using standard phosphoramidite chemistry with oxidation by iodine.

[00185] Phosphorothioates (P=S) are synthesized as for the phosphodiester oligonucleotides except the standard oxidation bottle is replaced by 0.2 M solution of 3H-1,2-benzodithiole-3-one 1,1-dioxide in acetonitrile for the stepwise thiation of the phosphite linkages. The thiation wait step is increased to 68 sec and is followed by the capping step. After cleavage from the CPG column and deblocking in concentrated ammonium hydroxide at 55°C (18 h), the oligonucleotides are purified by precipitating twice with 2.5 volumes of ethanol from a 0.5 M NaCl solution. Phosphinate oligonucleotides are prepared as described in U.S. Patent 5,508,270, herein incorporated by reference.

[00186] Alkyl phosphonate oligonucleotides are prepared as described in U.S. Patent 4,469,863, herein incorporated by reference.

[00187] 3'-Deoxy-3'-methylene phosphonate oligonucleotides are prepared as described in U.S. Patents 5,610,289 or 5,625,050, herein incorporated by reference.

[00188] Phosphoramidite oligonucleotides are prepared as described in U.S. Patent, 5,256,775 or U.S. Patent 5,366,878, herein incorporated by reference.

[00189] Alkylphosphonothioate oligonucleotides are prepared as described in WO 94/17093 and WO 94/02499 herein incorporated by reference.

[00190] 3'-Deoxy-3'-amino phosphoramidate oligonucleotides are prepared as described in U.S. Patent 5,476,925, herein incorporated by reference.

[00191] Phosphotriester oligonucleotides are prepared as described in U.S. Patent 5,023,243, herein incorporated by reference.

[00192] Borano phosphate oligonucleotides are prepared as described in U.S. Patents 5,130,302 and 5,177,198, both herein incorporated by reference.

Example 3

Oligonucleoside Synthesis

[00193] Methylenemethylimino linked oligonucleosides, also identified as MMI linked oligonucleosides, methylenedimethylhydrazo linked oligonucleosides, also identified as MDH linked oligonucleosides, and methylenecarbonylamino linked oligonucleosides, also identified as amide-3 linked oligonucleosides, and methyleneaminocarbonyl linked oligonucleosides, also identified as amide-4 linked oligonucleosides, as well as mixed backbone compounds having, for instance, alternating MMI and P=O or P=S linkages are prepared as described in U.S. Patents 5,378,825; 5,386,023; 5,489,677; 5,602,240; and 5,610,289, all of which are herein incorporated by reference.

[00194] Formacetal and thioformacetal linked oligonucleosides are prepared as described in U.S. Patents 5,264,562 and 5,264,564, herein incorporated by reference.

[00195] Ethylene oxide linked oligonucleosides are prepared as described in U.S. Patent 5,223,618, herein incorporated by reference.

Example 4

PNA Synthesis

[00196] Peptide nucleic acids (PNAs) are prepared in accordance with any of the various procedures referred to in Peptide Nucleic Acids (PNA): Synthesis, Properties and Potential Applications, *Bioorganic & Medicinal Chemistry*, 1996, 4, 523. They may also be prepared in accordance with U.S. Patents 5,539,082; 5,700,922; and 5,719,262, herein incorporated by reference.

Example 5

Synthesis of Chimeric Oligonucleotides

[00197] Chimeric oligonucleotides, oligonucleosides, or mixed oligonucleotides/oligonucleosides of the invention can be of several different types. These include a first type wherein the "gap" segment of linked nucleosides is positioned between 5' and 3' "wing" segments of linked nucleosides and a second "open end" type wherein the "gap"

segment is located at either the 3' or the 5' terminus of the oligomeric compound. Oligonucleotides of the first type are also known in the art as "gapmers" or gapped oligonucleotides. Oligonucleotides of the second type are also known in the art as "hemimers" or "wingmers".

2'-O-Me]--[2'-deoxy]--[2'-O-Me] Chimeric Phosphorothioate Oligonucleotides

[00198] Chimeric oligonucleotides having 2'-O-alkyl phosphorothioate and 2'-deoxy phosphorothioate oligonucleotide segments are synthesized using an Applied Biosystems automated DNA synthesizer Model 380B, as above. Oligonucleotides are synthesized using the automated synthesizer and 2'-deoxy-5'-dimethoxytrityl-3'-O-phosphoramidite for the DNA portion and 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite for 5' and 3' wings. The standard synthesis cycle is modified by increasing the wait step after the delivery of tetrazole and base to 600 s repeated four times for RNA and twice for 2'-O-methyl. The fully protected oligonucleotide is cleaved from the support and the phosphate group is deprotected in 3:1 ammonia/ethanol at room temperature overnight then lyophilized to dryness. Treatment in methanolic ammonia for 24 hrs at room temperature is then done to deprotect all bases and sample is again lyophilized to dryness. The pellet is resuspended in 1M TBAF in THF for 24 hrs at room temperature to deprotect the 2' positions. The reaction is then quenched with 1M TEAA and the sample is then reduced to 1/2 volume by rotovac before being desalted on a G25 size exclusion column. The oligo recovered is then analyzed spectrophotometrically for yield and for purity by capillary electrophoresis and by mass spectrometry.

[00199] [2'-O-(2-Methoxyethyl)]--[2'-deoxy]--[2'-O-(Methoxyethyl)] Chimeric Phosphorothioate Oligonucleotides

[00200] [2'-O-(2-methoxyethyl)]--[2'-deoxy]—[-2'-O-(methoxyethyl)] chimeric phosphorothioate oligonucleotides are prepared as per the procedure above for the 2'-O-methyl chimeric oligonucleotide, with the substitution of phorothioate oligonucleotides

are prepared as per the procedure above for 2'-O-(methoxyethyl) amidites for the 2'-O-methyl amidites.

[2'-O-(2-Methoxyethyl)Phosphodiester]--[2'-deoxy Phosphorothioate]--[2'-O-(2-Methoxyethyl)] Phosphodiester] Chimeric Oligonucleotides

[00201] [2'-O-(2-methoxyethyl phosphodiester]--[2'-deoxy phosphorothioate]--[2'-O-(methcixyethyl) phosphodiester] chimeric oligonucleotides are prepared as per the above procedure for the 2'-O-methyl chimeric oligonucleotide with the substitution of 2'-O-(methoxyethyl) amidites for the 2'-O-methyl amidites, oxidization with iodine to generate the phosphodiester internucleotide linkages within the wing portions of the chimeric structures and sulfurization utilizing 3,H-1,2 benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) to generate the phosphorothioate internucleotide linkages for the center gap.

[00202] Other chimeric oligonucleotides, chimeric oligonucleosides, and mixed chimeric oligonucleotides/oligonucleosides are synthesized according to United States patent 5,623,065, herein incorporated by reference.

Example 6

Oligonucleotide Isolation

[00203] After cleavage from the controlled pore glass column (Applied Biosystems) and deblocking in concentrated ammonium hydroxide at 55°C for 18 hours, the oligonucleotides or oligonucleosides are purified by precipitation twice out of 0.5 M NaCl with 2.5 volumes ethanol. Synthesized oligonucleotides are analyzed by polyacrylamide gel electrophoresis on denaturing gels and judged to be at least 85% full-length material. The relative amounts of phosphorothioate and phosphodiester linkages obtained in synthesis are periodically checked by "P nuclear magnetic resonance spectroscopy, and for some studies oligonucleotides are purified by HPLC, as described by Chiang et al., *J. Biol. Chem.* 1991, 266, 18162-18171.

Example 7

Oligonucleotide Synthesis - 96 Well Plate Format

[00204] Oligonucleotides are synthesized via solid phase P(III) phosphoramidite chemistry on an automated synthesizer capable of assembling 96 sequences simultaneously in a standard 96 well format. Phosphodiester internucleotide linkages are afforded by oxidation with aqueous iodine. Phosphorothioate internucleotide linkages are generated by sulfurization utilizing 3,H-1,2 benzodithiole-3-one 1,1 dioxide (Beaucage Reagent) in anhydrous acetonitrile. Standard base-protected beta-cyanoethyldiisopropyl phosphoramidites can be purchased from commercial vendors (e.g. PE-Applied Biosystems, Foster City, CA, or Pharmacia, Piscataway, NJ). Non-standard nucleosides are synthesized as per known literature or patented methods. They are utilized as base protected betacyanoethyldiisopropyl phosphoramidites.

[00205] Oligonucleotides are cleaved from support and deprotected with concentrated NH_4OH at elevated temperature (55-60°C) for 12-16 hours and the released product then dried in vacuo. The dried product is then re-suspended in sterile water to afford a master plate from which all analytical and test plate samples are then diluted utilizing robotic pipettors.

Example 8

Oligonucleotide Analysis - 96 Well Plate Format

[00206] The concentration of oligonucleotide in each well is assessed by dilution of samples and UV absorption spectroscopy. The full-length integrity of the individual products is evaluated by capillary electrophoresis (CE) in either the 96 well format (Beckman P/ACE™ MDQ) or, for individually prepared samples, on a commercial CE apparatus (e.g., Beckman P/ACE™ 5000, ABI 270). Base and backbone composition is confirmed by mass analysis of the compounds utilizing electrospray-mass spectroscopy. All assay test plates are diluted from the master plate using single and multi-channel robotic pipettors. Plates

are judged to be acceptable if at least 85% of the compounds on the plate are at least 85% full length.

Example 9

Cell culture and oligonucleotide treatment

[00207] The effect of antisense compounds on target nucleic acid expression can be tested in any of a variety of cell types provided that the target nucleic acid is present at measurable levels. This can be routinely determined using, for example, PCR or Northern blot analysis. The following 6 cell types are provided for illustrative purposes, but other cell types can be routinely used, provided that the target is expressed in the cell type chosen. This can be readily determined by methods routine in the art, for example Northern blot analysis, Ribonuclease protection assays, or RT-PCR.

T-24 cells:

[00208] The human transitional cell bladder carcinoma cell line T-24 is obtained from the American Type Culture Collection (ATCC) (Manassas, VA). T-24 cells are routinely cultured in complete McCoy's 5A basal media (Gibco/Life Technologies, Gaithersburg, MD) supplemented with 10% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Gibco/Life Technologies, Gaithersburg, MD). Cells are routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells are seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

[00209] For Northern blotting or other analysis, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

A549 cells:

[00210] The human lung carcinoma cell line A549 can be obtained from the American Type Culture Collection (ATCC) (Manassas, VA). A549 cells are routinely cultured in DMEM basal media (Gibco/Life

Technologies, Gaithersburg, MD) supplemented with 10% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD), penicillin 100 units per mL, and streptomycin 100 micrograms per mL (Gibco/Life Technologies, Gaithersburg, MD). Cells are routinely passaged by trypsinization and dilution when they reached 90% confluence.

NHDF cells:

[00211] Human neonatal dermal fibroblast (NHDF) can be obtained from the Clonetics Corporation (Walkersville MD). NHDFs are routinely maintained in Fibroblast Growth Medium (Clonetics Corporation, Walkersville MD) supplemented as recommended by the supplier. Cells are maintained for up to 10 passages as recommended by the supplier.

HEK cells:

[00212] Human embryonic keratinocytes (HEK) can be obtained from the Clonetics Corporation (Walkersville MD). HEKs are routinely maintained in Keratinocyte Growth Medium (Clonetics Corporation, Walkersville MD) formulated as recommended by the supplier. Cells are routinely maintained for up to 10 passages as recommended by the supplier.

MCF-7 cells:

[00213] The human breast carcinoma cell line MCF-7 is obtained from the American Type Colure Collection (Manassas, VA). MCF-7 cells are routinely cultured in DMEM low glucose (Gibco/Life Technologies, Gaithersburg, MD) supplemented with 10% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD). Cells are routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells are seeded into 96-well plates (Falcon-Primaria #3872) at a density of 7000 cells/well for use in RT-PCR analysis.

[00214] For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

LA4 cells:

[00215] The mouse lung epithelial cell line LA4 is obtained from the American Type Colure Collection (Manassas, VA). LA4 cells are routinely cultured in F12K medium (Gibco/Life Technologies, Gaithersburg, MD) supplemented with 15% fetal calf serum (Gibco/Life Technologies, Gaithersburg, MD). Cells are routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells are seeded into 96-well plates (Falcon-Primaria #3872) at a density of 3000-6000 cells/ well for use in RT-PCR analysis.

[00216] For Northern blotting or other analyses, cells may be seeded onto 100 mm or other standard tissue culture plates and treated similarly, using appropriate volumes of medium and oligonucleotide.

Treatment with antisense compounds:

[00217] When cells reached 80% confluence, they are treated with oligonucleotide. For cells grown in 96-well plates, wells are washed once with 200 µL OPTI-MEM™-1 reduced-serum medium (Gibco BRL) and then treated with 130 µL of OPTI-MEM™-1 containing 3.75 µg/mL LIPOFECTIN™ (Gibco BRL) and the desired concentration of oligonucleotide. After 4-7 hours of treatment, the medium is replaced with fresh medium. Cells are harvested 16-24 hours after oligonucleotide treatment.

[00218] The concentration of oligonucleotide used varies from cell line to cell line. To determine the optimal oligonucleotide concentration for a particular cell line, the cells are treated with a positive control oligonucleotide at a range of concentrations.

Example 10

Analysis of oligonucleotide inhibition of ESM-1 expression

[00219] Antisense modulation of ESM-1 expression can be assayed in a variety of ways known in the art. For example, ESM-1 mRNA levels can be quantitated by, e.g., Northern blot analysis, competitive polymerase chain reaction (PCR), or real-time PCR (RT-PCR). Real-time quantitative PCR is presently preferred. RNA analysis can be performed on total cellular RNA or poly(A)+ mRNA. Methods of RNA

isolation are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.1.1-4.2.9 and 4.5.1-4.5.3, John Wiley & Sons, Inc., 1993. Northern blot analysis is routine in the art and is taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.2.1-4.2.9, John Wiley & Sons, Inc., 1996. Real-time quantitative (PCR) can be conveniently accomplished using the commercially available ABI PRISM™ 7700 Sequence Detection System, available from PE-Applied Biosystems, Foster City, CA and used according to manufacturer's instructions. Prior to quantitative PCR analysis, primer-probe sets specific to the target gene being measured are evaluated for their ability to be "multiplexed" with a GAPDH amplification reaction. In multiplexing, both the target gene and the internal standard gene GAPDH are amplified concurrently in a single sample. In this analysis, mRNA isolated from untreated cells is serially diluted. Each dilution is amplified in the presence of primer-probe sets specific for GAPDH only, target gene only ("single-plexing"), or both (multiplexing). Following PCR amplification, standard curves of GAPDH and target mRNA signal as a function of dilution are generated from both the single-plexed and multiplexed samples. If both the slope and correlation coefficient of the GAPDH and target signals generated from the multiplexed samples fall within 10% of their corresponding values generated from the single-plexed samples, the primer-probe set specific for that target is deemed as multiplexable. Other methods of PCR are also known in the art.

[00220] Protein levels of ESM-1 can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), ELISA or fluorescence-activated cell sorting (FACS). Antibodies directed to ESM-1 can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional antibody generation methods. Methods for preparation of polyclonal antisera are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.12.1-11.12.9, John

Wiley & Sons, Inc., 1997. Preparation of monoclonal antibodies is taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.4.1-11.11.5, John Wiley Sons, Inc., 1997.

[00221] Immunoprecipitation methods are standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 10.16.110.16.11, John Wiley & Sons, Inc., 1998. Western blot (immunoblot) analysis is standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 10.8.1-10.8.21, John Wiley Sons, Inc., 1997. Enzyme-linked immunosorbent assays (ELISA) are standard in the art and can be found at, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 2, pp. 11.2.1-11.2.22, John Wiley & Sons, Inc., 1991.

Example 11

Poly(A)+ mRNA isolation

[00222] Poly(A)+ mRNA is isolated according to Miura et al., *Clin. Chem.*, 1996, 42, 1758-1764. Other methods for poly(A)+ mRNA isolation are taught in, for example, Ausubel, F.M. et al., *Current Protocols in Molecular Biology*, Volume 1, pp. 4.5.1-4.5.3, John Wiley & Sons, Inc., 1993. Briefly, for cells grown on 96-well plates, growth medium is removed from the cells and each well is washed with 200 µL cold PBS. 60µL lysis buffer (10 mM Tris-HCl, pH 7.6, 1 mM EDTA, 0.5 M NaCl, 0.5% NP-40, 20 mM vanadyl-ribonucleoside complex) is added to each well, the plate is gently agitated and then incubated at room temperature for five minutes. 55 µL of lysate is transferred to Oligo d(T) coated 96-well plates (AGCT Inc., Irvine CA). Plates are incubated for 60 minutes at room temperature, washed 3 times with 200 µL of wash buffer (10 mM Tris-HC1 pH 7.6, 1 mM EDTA, 0.3 M NaCl). After the final wash, the plate is blotted on paper towels to remove excess wash buffer and then air-dried for 5 minutes. 60 pL of elution buffer (5 mM Tris-HCl pH 7.6), preheated to 70°C is added to

each well, the plate is incubated on a 90°C hot plate for 5 minutes, and the eluate is then transferred to a fresh 96-well plate.

[00223] Cells grown on 100 mm or other standard plates may be treated similarly, using appropriate volumes of all solutions.

Example 12

Total RNA Isolation

[00224] Total mRNA is isolated using an RNEASY 96™ kit and buffers purchased from Qiagen Inc. (Valencia CA) following the manufacturer's recommended procedures. Briefly, for cells grown on 96-well plates, growth medium is removed from the cells and each well is washed with 200 µL cold PBS. 100 µL Buffer RLT is added to each well and the plate vigorously agitated for 20 seconds. 100 µL of 70% ethanol is then added to each well and the contents mixed by pipetting three times up and down. The samples are then transferred to the RNEASY 96™ well plate attached to a QIAVAC™ manifold fitted with a waste collection tray and attached to a vacuum source. Vacuum is applied for 15 seconds. 1 mL of Buffer RW1 is added to each well of the RNEASY 96™ plate and the vacuum again applied for 15 seconds. 1 mL of Buffer RPE is then added to each well of the RNEASY 96™ plate and the vacuum applied for a period of 15 seconds. The Buffer RPE wash is then repeated and the vacuum is applied for an additional 10 minutes. The plate is then removed from the QIAVAC™ manifold and blotted dry on paper towels. The plate is then re-attached to the QIAVAC™ manifold fitted with a collection tube rack containing 1.2 mL collection tubes. RNA is then eluted by pipetting 60µL water into each well, incubating one minute, and then applying the vacuum for 30 seconds. The elution step is repeated with an additional 60µL water.

[00225] The repetitive pipetting and elution steps may be automated using a QIAGEN Bio-Robot 9604 (Qiagen, Inc., Valencia CA). Essentially, after lysing of the cells on the culture plate, the plate is transferred to the robot deck where the pipetting, DNase treatment and elution steps are carried out.

Example 13

Real-time Quantitative PCR Analysis of ESM-1 mRNA Levels

[00226] Real-time quantitative reverse transcription polymerase chain reaction experiments show ESM-1 mRNA expression at levels of threefold or higher at the mRNA level in nine out of ten tumors when compared to the normal tissue (Figure 2). Quantitation of ESM-1 mRNA levels were determined by real-time quantitative PCR using the ABI PRISM™ 7700 Sequence Detection System (PE-Applied Biosystems, Foster City, CA) according to manufacturer's instructions. This is a closed-tube, non-gel-based, fluorescence detection system which allows high-throughput quantitation of polymerase chain reaction (PCR) products in real-time. As opposed to standard PCR, in which amplification products are quantitated after the PCR is completed, products in real-time quantitative PCR are quantitated as they accumulate. This is accomplished by including in the PCR reaction an oligonucleotide probe that anneals specifically between the forward and reverse PCR primers, and contains two fluorescent dyes. A reporter dye (e.g., JOE, FAM™, or VIC, obtained from either Operon Technologies Inc., Alameda, CA or PE-Applied Biosystems, Foster City, CA) is attached to the 5' end of the probe and a quencher dye (e.g., TAMRA, obtained from either Operon Technologies Inc., Alameda, CA or PE-Applied Biosystems, Foster City, CA) is attached to the 3' end of the probe. When the probe and dyes are intact, reporter dye emission is quenched by the proximity of the 3' quencher dye. During amplification, annealing of the probe to the target sequence creates a substrate that can be cleaved by the 5'-exonuclease activity of Taq polymerase. During the extension phase of the PCR amplification cycle, cleavage of the probe by Taq polymerase releases the reporter dye from the remainder of the probe (and hence from the quencher moiety) and a sequence-specific fluorescent signal is generated. With each cycle, additional reporter dye molecules are cleaved from their respective probes, and the fluorescence intensity is monitored at regular intervals by laser optics built into the

ABI PRISM™ 7700 Sequence Detection System. In each assay, a series of parallel reactions containing serial dilutions of mRNA from untreated control samples generates a standard curve that is used to quantitate the percent inhibition after antisense oligonucleotide treatment of test samples.

[00227] PCR reagents were obtained from PE-Applied Biosystems, Foster City, CA. RT-PCR reactions were carried out by adding 25μL PCR cocktail (1x TAQMAN™ buffer A, 5.5 MM $MgCl_2$, 300 μM each of dATP, dCTP and dGTP, 600 μM of dUTP, 100 nM each of forward primer, reverse primer, and probe, 20 Units RNAse inhibitor, 1.25 Units AMPLITAQ GOLD™, and 12.5 Units MuLV reverse transcriptase) to 96 well plates containing 25 μL poly(A) mRNA solution. The RT reaction was carried out by incubation for 30 minutes at 48°C. Following a 10 minute incubation at 95°C to activate the AMPLITAQ GOLD™, 40 cycles of a two-step PCR protocol were carried out: 95°C for 15 seconds (denaturation) followed by 60°C for 1.5 minutes (annealing/extension).

[00228] Probes and primers to human ESM-1 were designed to hybridize to a human ESM-1 sequence, using published sequence, information (GenBank accession number NM_007036, incorporated herein as Figure 1. For human ESM-1 the PCR primers were:

forward primer: CTGCTTCCCACCAGCAAAG SEQ ID NO:2001

reverse primer: GCAAGACGCTCTTCATGTTTCC SEQ ID NO:2002

and the PCR probe is: FAM™- CGACTGGAGAGCCGAGCCGGA SEQ ID NO;2003 -TAMRA where FAM™ (PE-Applied Biosystems, Foster City, CA) is the fluorescent reporter dye) and TAMRA (PE-Applied Biosystems, Foster City, CA) is the quencher dye. For human cyclophilin the PCR primers were:

forward primer: CCCACCGTGTTCTTCGACAT SEQ ID NO:2004

reverse primer: TTTCTGCTGTCTTTGGGACCTT SEQ ID NO:2005

and the PCR probe is: 5' JOE- CGCGTCTCCTTTGAGCTGTTTGCA SEQ ID NO:2006 - TAMRA 3' where JOE (PE-Applied Biosystems,

Foster City, CA) is the fluorescent reporter dye) and TAMRA (PE-Applied Biosystems, Foster City, CA) is the quencher dye.

Example 14

Antisense inhibition of human ESM-1 expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

[00229] In accordance with the present invention, a series of oligonucleotides are designed to target different regions of the human ESM-1 RNA, using published sequences (NM_007036, incorporated herein as Figure 1. The oligonucleotides are shown in Table 1. "Position" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. The indicated parameters for each oligo were predicted using RNAstructure 3.7 by David H. Mathews, Michael Zuker, and Douglas H. Turner. The parameters are described either as free energy (The energy that is released when a reaction occurs. The more negative the number, the more likely the reaction will occur. All free energy units are in kcal/mol.) or melting temperature (temperature at which two anneal strands of polynucleic acid separate). The higher the temperature, the greater the affinity between the two strands. When designing an antisense oligonucleotide that will bind with high affinity, it is desirable to consider the structure of the target RNA strand and the antisense oligomer. Specifically, for an oligomer to bind tightly (in the table described as 'duplex formation'), it should be complementary to a stretch of target RNA that has little self-structure (in the table the free energy of which is described as 'target structure'). Also, the oligomer should have little self-structure, either intramolecular (in the table the free energy of which is described as 'intramolecular oligo') or bimolecular (in the table the free energy of which is described as 'intermolecular oligo'). Breaking up any self-structure amounts to a binding penalty. All compounds in Table 1 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a

central "gap" region consisting of ten 2'deoxynucleotides, which is flanked on both sides (5' and 3' directions) by four-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. Cytidine residues in the 2'-MOE wings are 5-methylcytidines. All cytidine residues are 5-methylcytidines.

TABLE 1

position	oligo	kcal/ mol total binding	kcal/ mol duplex form-ation	deg C Tm of Duplex	kcal/ mol target struc-ture	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
31	GCTCGGCTCTCCAGTCGTGG SEQ ID NO;1	-25.9	-31	85.7	-3.4	-1.7	-7.1
32	GGCTCGGCTCTCCAGTCGTG SEQ ID NO;2	-25.9	-31	85.7	-3.4	-1.7	-9.6
28	CGGCTCTCCAGTCGTGGTCT SEQ ID NO;3	-25.7	-30.4	84.9	-3.4	-1.2	-6.1
30	CTCGGCTCTCCAGTCGTGGT SEQ ID NO;4	-25.3	-30.4	84.9	-3.4	-1.7	-6.1
923	GCCTAGCTCCCTCTTTGGTT SEQ ID NO;5	-25.3	-30.4	85.5	-5.1	0	-6.2
33	CGGCTCGGCTCTCCAGTCGT SEQ ID NO;6	-25.1	-31.8	85.2	-4.7	-2	-9.6
27	GGCTCTCCAGTCGTGGTCTT SEQ ID NO;7	-25	-29.7	86.1	-3.4	-1.2	-6.1
928	GCTTTGCCTAGCTCCCTCTT SEQ ID NO;8	-24.9	-30.7	85.6	-5.1	-0.4	-6.2
29	TCGGCTCTCCAGTCGTGGTC SEQ ID NO;9	-24.8	-29.9	84.8	-3.4	-1.7	-6.1
924	TGCCTAGCTCCCTCTTTGGT SEQ ID NO;10	-24.6	-30.3	84.8	-5.1	-0.3	-4.6
26	GCTCTCCAGTCGTGGTCTTT SEQ ID NO;11	-24.4	-28.6	83.7	-3.4	-0.6	-5.2
929	AGCTTTGCCTAGCTCCCTCT SEQ ID NO;12	-24.2	-30.6	85.6	-5.1	-1.2	-7.7
930	CAGCTTTGCCTAGCTCCCTC SEQ ID NO;13	-23.9	-30.4	84.6	-5.1	-1.3	-7.8
931	TCAGCTTTGCCTAGCTCCCT SEQ ID NO;14	-23.9	-30.4	84.6	-5.1	-1.3	-7.8
1265	ACCGTCCTTCAGATACAGGT SEQ ID NO;15	-23.9	-26.3	74.5	-1.9	-0.1	-4.5
240	GTTTCTCCCCGCCCTGCAGC SEQ ID NO;16	-23.6	-34.9	90.4	-10.6	-0.4	-8.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
925	TTGCCTAGCTCCCTCTTTGG SEQ ID NO;17	-23.5	-29.2	81.5	-5.1	-0.3	-4.8
1264	CCGTCCTTCAGATACAGGTA SEQ ID NO;18	-23.4	-25.8	73.4	-1.9	-0.1	-3.9
927	CTTTGCCTAGCTCCCTCTTT SEQ ID NO;19	-23.3	-29	81.5	-5.1	-0.3	-4.8
932	TTCAGCTTTGCCTAGCTCCC SEQ ID NO;20	-23.1	-29.6	83	-5.1	-1.3	-7.8
241	AGTTTCTCCCCGCCCTGCAG SEQ ID NO;21	-23	-33.1	86.5	-9.4	-0.4	-7.8
243	CAAGTTTCTCCCCGCCCTGC SEQ ID NO;22	-23	-32.4	83.6	-9.4	0	-2.8
244	GCAAGTTTCTCCCCGCCCTG SEQ ID NO;23	-23	-32.4	83.6	-9.4	0	-3.4
245	AGCAAGTTTCTCCCCGCCCT SEQ ID NO;24	-23	-32.4	84.1	-9.4	0	-4.1
926	TTTGCCTAGCTCCCTCTTTG SEQ ID NO;25	-22.4	-28.1	79.3	-5.1	-0.3	-4.8
242	AAGTTTCTCCCCGCCCTGCA SEQ ID NO;26	-22.3	-32.4	83.6	-9.4	-0.4	-4.7
20	CAGTCGTGGTCTTTGCTGGT SEQ ID NO;27	-22	-27.3	80	-5.3	0	-3.6
246	TAGCAAGTTTCTCCCCGCCC SEQ ID NO;28	-21.8	-31.2	81.8	-9.4	0	-4.1
21	CCAGTCGTGGTCTTTGCTGG SEQ ID NO;29	-21.7	-28.1	80	-5.3	-1	-5.3
23	CTCCAGTCGTGGTCTTTGCT SEQ ID NO;30	-21.6	-28.2	81.4	-5.3	-1.2	-6
34	CCGGCTCGGCTCTCCAGTCG SEQ ID NO;31	-21.5	-32.6	84.9	-8.9	-2.2	-8.5
19	AGTCGTGGTCTTTGCTGGTG SEQ ID NO;32	-21.3	-26.6	78.7	-5.3	0	-3.6
199	GTCGTCGAGCACTGTCCTCT SEQ ID NO;33	-21.2	-28.8	81.5	-7	-0.3	-4.9
24	TCTCCAGTCGTGGTCTTTGC SEQ ID NO;34	-21.1	-27.7	81.3	-5.3	-1.2	-5
247	GTAGCAAGTTTCTCCCCGCC SEQ ID NO;35	-21	-30.4	81.9	-9.4	0	-4.1
1024	CCTCCCCATCTTCTCCTGCT SEQ ID NO;36	-21	-32.7	87.6	-11.7	0	-3.6
200	AGTCGTCGAGCACTGTCCTC SEQ ID NO;37	-20.9	-27.9	79.9	-7	0	-5.3
191	GCACTGTCCTCTTGCAGCGC SEQ ID NO;38	-20.8	-30.4	84.4	-8.7	-0.8	-8
22	TCCAGTCGTGGTCTTTGCTG SEQ ID NO;39	-20.7	-27.3	79.1	-5.3	-1.2	-6
196	GTCGAGCACTGTCCTCTTGC SEQ ID NO;40	-20.7	-28.3	81.2	-7	-0.3	-5.7
198	TCGTCGAGCACTGTCCTCTT SEQ ID NO;41	-20.7	-27.7	78.3	-7	0.2	-4.9
922	CCTAGCTCCCTCTTTGGTTG SEQ ID NO;42	-20.7	-28.6	80.6	-7.9	0	-6.2
1263	CGTCCTTCAGATACAGGTAA SEQ ID NO;43	-20.7	-23.1	67.4	-1.9	-0.1	-3.9
35	TCCGGCTCGGCTCTCCAGTC SEQ ID NO;44	-20.6	-32.2	87.6	-10.1	-1.4	-8.5
1023	CTCCCCATCTTCTCCTGCTC SEQ ID NO;45	-20.5	-31.1	86.1	-10.6	0	-3.6
201	CAGTCGTCGAGCACTGTCCT SEQ ID NO;46	-20.4	-28.2	79.1	-7	-0.5	-8.4

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
36	CTCCGGCTCGGCTCTCCAGT SEQ ID NO;47	-20.1	-32.7	87.6	-11.1	-1.4	-8.5
327	CCAAAAGGATCCTCCCCATT SEQ ID NO;48	-20	-26.9	70.9	-5.8	-0.9	-9.4
328	ACCAAAAGGATCCTCCCCAT SEQ ID NO;49	-20	-27	71	-5.8	-0.9	-9.9
190	CACTGTCCTCTTGCAGCGCG SEQ ID NO;50	-19.8	-29.4	79.5	-8.7	-0.6	-9
919	AGCTCCCTCTTTGGTTGACC SEQ ID NO;51	-19.8	-28.8	81.2	-9	0	-5.7
197	CGTCGAGCACTGTCCTCTTG SEQ ID NO;52	-19.7	-27.3	76.3	-7	-0.3	-4.9
1022	TCCCCATCTTCTCCTGCTCT SEQ ID NO;53	-19.6	-31.1	86.1	-11.5	0	-3.6
239	TTTCTCCCCGCCCTGCAGCG SEQ ID NO;54	-19.2	-34.5	86.2	-13.7	-1.5	-9.4
18	GTCGTGGTCTTTGCTGGTGG SEQ ID NO;55	-19.1	-27.8	81.1	-8.7	0	-3.6
248	GGTAGCAAGTTTCTCCCCGC SEQ ID NO;56	-19	-29.6	81	-10.6	0	-4.1
1266	AACCGTCCTTCAGATACAGG SEQ ID NO;57	-18.8	-24.4	68.9	-5.6	0	-4
1025	CCCTCCCCATCTTCTCCTGC SEQ ID NO;58	-18.7	-33.8	88.9	-15.1	0	-2.6
202	ACAGTCGTCGAGCACTGTCC SEQ ID NO;59	-18.6	-27.5	77.7	-7	-1.8	-11
442	TTTCAGGCATTTTCCCGTCC SEQ ID NO;60	-18.5	-28.1	78	-9.6	0.7	-4
1538	TTATCATGCCTCAGATGTTT SEQ ID NO;61	-18.5	-22.7	68	-4.2	0	-4.4
1539	TTTATCATGCCTCAGATGTT SEQ ID NO;62	-18.5	-22.7	68	-4.2	0	-3.8
1021	CCCCATCTTCTCCTGCTCTT SEQ ID NO;63	-18.4	-30.8	84.6	-12.4	0	-3.6
1531	GCCTCAGATGTTTGAAAACC SEQ ID NO;64	-18.4	-22.5	64.6	-3.6	-0.1	-5.7
1537	TATCATGCCTCAGATGTTTG SEQ ID NO;65	-18.4	-22.6	67.5	-4.2	0	-4.4
192	AGCACTGTCCTCTTGCAGCG SEQ ID NO;66	-18.3	-28.6	80.3	-8.7	-1.6	-6.5
585	TTCCTCATTACGGGAGACCC SEQ ID NO;67	-18.3	-27.1	74.2	-7.4	-1.3	-5.5
936	GGTCTTCAGCTTTGCCTAGC SEQ ID NO;68	-18.3	-28	82.3	-9	-0.4	-6.2
1352	AGTGGGTAAAATACTTCTTA SEQ ID NO;69	-18.2	-18.4	57.7	0	0.6	-3.7
37	CCTCCGGCTCGGCTCTCCAG SEQ ID NO;70	-18.1	-33.5	87.2	-13.9	-1.4	-8.5
193	GAGCACTGTCCTCTTGCAGC SEQ ID NO;71	-18.1	-28.4	82.2	-8.7	-1.6	-5.5
915	CCCTCTTTGGTTGACCTGTC SEQ ID NO;72	-18.1	-28.2	79.8	-10.1	0	-6.7
1351	GTGGGTAAAATACTTCTTAG SEQ ID NO;73	-17.9	-18.4	57.7	0	-0.2	-3.3
326	CAAAAGGATCCTCCCCATTA SEQ ID NO;74	-17.8	-24.6	67.1	-5.8	-0.1	-9.9
437	GGCATTTTCCCGTCCCCCTG SEQ ID NO;75	-17.7	-33.7	85.7	-16	0	-4
443	ATTTCAGGCATTTTCCCGTC SEQ ID NO;76	-17.7	-26.1	74.4	-7.9	-0.1	-4

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
533	CAATATTGCCATCTCCAGAT SEQ ID NO;77	-17.7	-23.3	66.8	-5.6	0	-6.8
921	CTAGCTCCCTCTTTGGTTGA SEQ ID NO;78	-17.7	-27.2	78.4	-9.5	0	-6.2
1597	GCTCATTTTTTGACATTTTT SEQ ID NO;79	-17.6	-20.2	62.5	-2.1	-0.1	-2.6
238	TTCTCCCCGCCCTGCAGCGC SEQ ID NO;80	-17.5	-36.2	89.8	-17	-1.7	-9.7
1027	CCCCCTCCCCATCTTCTCCT SEQ ID NO;81	-17.5	-36	91.2	-18.5	0	-0.5
1598	TGCTCATTTTTTGACATTTT SEQ ID NO;82	-17.5	-20.1	62.1	-2.1	-0.1	-3.3
329	CACCAAAAGGATCCTCCCCA SEQ ID NO;83	-17.4	-27.7	72.1	-9.1	-0.9	-9.9
1599	TTGCTCATTTTTTGACATTT SEQ ID NO;84	-17.4	-20.1	62.1	-2.1	-0.2	-3.3
534	ACAATATTGCCATCTCCAGA SEQ ID NO;85	-17.3	-23.5	67.4	-5.6	0	-8.5
1349	GGGTAAAATACTTCTTAGAT SEQ ID NO;86	-17.3	-17.8	56.1	0	-0.2	-4.3
1350	TGGGTAAAATACTTCTTAGA SEQ ID NO;87	-17.3	-17.8	56.1	0	-0.2	-4.3
438	AGGCATTTTCCCGTCCCCCT SEQ ID NO;88	-17.2	-33.7	86.3	-16	-0.1	-4
194	CGAGCACTGTCCTCTTGCAG SEQ ID NO;89	-17.1	-27.4	77.2	-8.7	-1.6	-6.5
469	GGTTACTGAATATTGGAAGA SEQ ID NO;90	-17.1	-18.7	57.9	-1.6	0	-4.6
678	AAAGTTCCTAAAATGTTGGC SEQ ID NO;91	-17.1	-19.1	57.8	-2	0	-3.1
937	CGGTCTTCAGCTTTGCCTAG SEQ ID NO;92	-17.1	-27	77.1	-9.9	0	-4.5
1032	TCCCACCCCCTCCCCATCTT SEQ ID NO;93	-17.1	-36.7	90.2	-19.6	0	-0.5
914	CCTCTTTGGTTGACCTGTCT SEQ ID NO;94	-17	-27.1	78.2	-10.1	0	-6.7
364	GCCGTAGGGACAGTCTTTGC SEQ ID NO;95	-16.8	-27.9	79.2	-9.5	-1.5	-8.4
586	TTTCCTCATTACGGGAGACC SEQ ID NO;96	-16.8	-25.2	71.1	-7.4	-0.9	-5.1
1028	ACCCCCTCCCCATCTTCTCC SEQ ID NO;97	-16.8	-35.3	90	-18.5	0	-0.5
25	CTCTCCAGTCGTGGTCTTTG SEQ ID NO:98	-16.7	-26.8	78.6	-8.8	-1.2	-5
235	TCCCCGCCCTGCAGCGCACA SEQ ID NO:99	-16.7	-36.4	88.2	-18	-1.7	-10
1421	ATGACTTGCACTAACACATT SEQ ID NO:100	-16.7	-20.3	60.8	-3.6	0	-5
444	AATTTCAGGCATTTTCCCGT SEQ ID NO:101	-16.6	-25	70.4	-7.9	-0.1	-4
237	TCTCCCCGCCCTGCAGCGCA SEQ ID NO:102	-16.5	-36.8	90.3	-18.6	-1.7	-10.5
441	TTCAGGCATTTTCCCGTCCC SEQ ID NO:103	-16.5	-30	81.1	-13	-0.1	-3.3
1354	CCAGTGGGTAAAATACTTCT SEQ ID NO:104	-16.5	-21.3	63	-4.3	-0.2	-6.7
1262	GTCCTTCAGATACAGGTAAC SEQ ID NO:105	-16.4	-22.5	67.8	-5.6	-0.1	-3.9
1708	CTGCTGAAAATTGATTCTTC SEQ ID NO:106	-16.4	-18.7	57.7	-2.3	0.4	-3.6

position	oligo	kcal/ mol total binding	kcal/ mol duplex formation	deg C Tm of Duplex	kcal/ mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
539	CTCTCACAATATTGCCATCT SEQ ID NO:107	-16.3	-23.1	67.5	-6.2	0	-8.5
778	GGATGTTATGGATTGTAAGT SEQ ID NO:108	-16.3	-20.1	62.2	-3.8	0	-2.2
938	GCGGTCTTCAGCTTTGCCTA SEQ ID NO:109	-16.3	-28.8	81.3	-12.5	0	-4.5
1419	GACTTGCACTAACACATTTA SEQ ID NO:110	-16.3	-20.1	60.7	-3.8	0	-5
1420	TGACTTGCACTAACACATTT SEQ ID NO:111	-16.3	-20.4	61.1	-4.1	0	-4.7
1272	CCCCAGAACCGTCCTTCAGA SEQ ID NO:112	-16.2	-29.9	77.8	-13.7	0.6	-2.7
1348	GGTAAAATACTTCTTAGATT SEQ ID NO:113	-16.2	-16.7	53.9	0	-0.2	-4.3
189	ACTGTCCTCTTGCAGCGCGG SEQ ID NO:114	-16.1	-29.9	81	-12.9	-0.6	-9
393	CAGGTCTCTCTGCAATCCAT SEQ ID NO:115	-16.1	-25.9	75.1	-9.8	0	-4.9
677	AAGTTCCTAAAATGTTGGCT SEQ ID NO:116	-16.1	-20.7	61.5	-4.6	0	-3.9
769	GGATTGTAAGTATCCTACTT SEQ ID NO:117	-16.1	-21.2	64.5	-3.8	-1.2	-5.5
774	GTTATGGATTGTAAGTATCC SEQ ID NO:118	-16.1	-20.4	63.1	-3.8	-0.1	-4.4
939	TGCGGTCTTCAGCTTTGCCT SEQ ID NO:119	-16.1	-29.1	81.7	-12.3	-0.5	-4.5
940	CTGCGGTCTTCAGCTTTGCC SEQ ID NO:120	-16.1	-29.1	81.7	-12.3	-0.5	-4.5
1353	CAGTGGGTAAAATACTTCTT SEQ ID NO:121	-16.1	-19.4	59.6	-2.8	-0.2	-4.8
934	TCTTCAGCTTTGCCTAGCTC SEQ ID NO:122	-16	-26.9	79.6	-9.7	-1.1	-7.6
1605	CCTCTGTTGCTCATTTTTTG SEQ ID NO:123	-16	-23.8	70.9	-7.8	0	-3.6
17	TCGTGGTCTTTGCTGGTGGG SEQ ID NO:124	-15.9	-27.8	80.1	-11.9	0	-3.6
436	GCATTTTCCCGTCCCCCTGT SEQ ID NO:125	-15.9	-33.7	86.7	-17.8	0	-3.4
679	GAAAGTTCCTAAAATGTTGG SEQ ID NO:126	-15.9	-17.9	55.2	-2	0	-2.9
1267	GAACCGTCCTTCAGATACAG SEQ ID NO:127	-15.9	-23.8	67.7	-7.9	0	-3.1
1596	CTCATTTTTTGACATTTTTT SEQ ID NO:128	-15.9	-18.5	58.6	-2.1	-0.1	-2.6
1706	GCTGAAAATTGATTCTTCTT SEQ ID NO:129	-15.9	-18.8	58.1	-2.3	-0.3	-4.9
1903	ATTCACAACTCTGTTGGCCA SEQ ID NO:130	-15.9	-24.8	71.3	-7.8	-0.9	-9.5
203	CACAGTCGTCGAGCACTGTC SEQ ID NO:131	-15.8	-26.2	75.2	-8.3	-2	-11.2
1280	TTCCTATGCCCCAGAACCGT SEQ ID NO:132	-15.8	-29.7	77	-13.9	0	-3
1707	TGCTGAAAATTGATTCTTCT SEQ ID NO:133	-15.8	-18.7	57.7	-2.3	-0.3	-4.9
1709	TCTGCTGAAAATTGATTCTT SEQ ID NO:134	-15.8	-18.7	57.7	-2.3	-0.3	-4.7
1710	TTCTGCTGAAAATTGATTCT SEQ ID NO:135	-15.8	-18.7	57.7	-2.3	-0.3	-6.6
770	TGGATTGTAAGTATCCTACT SEQ ID NO:136	-15.7	-21.1	64.1	-3.8	-1.6	-5.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
912	TCTTTGGTTGACCTGTCTCC SEQ ID NO:137	-15.7	-26.6	78	-10.9	0	-6
917	CTCCCTCTTTGGTTGACCTG SEQ ID NO:138	-15.7	-27.9	78.2	-12.2	0	-6.7
1030	CCACCCCCTCCCCATCTTCT SEQ ID NO:139	-15.7	-35.6	89	-19.9	0	-0.5
1532	TGCCTCAGATGTTTGAAAAC SEQ ID NO:140	-15.7	-20.5	60.9	-4.8	0	-5.3
1026	CCCCTCCCCATCTTCTCCTG SEQ ID NO:141	-15.6	-34	87.8	-18.4	0	-1.4
1033	CTCCCACCCCCTCCCCATCT SEQ ID NO:142	-15.6	-37.5	91.6	-21.9	0	-0.5
1606	CCCTCTGTTGCTCATTTTTT SEQ ID NO:143	-15.6	-25.8	74.8	-10.2	0	-3.6
16	CGTGGTCTTTGCTGGTGGGA SEQ ID NO:144	-15.5	-28	79.6	-12.5	0	-3.6
764	GTAAGTATCCTACTTTTTGT SEQ ID NO:145	-15.5	-20.8	64.5	-3.8	-1.4	-5.1
781	TATGGATGTTATGGATTGTA SEQ ID NO:146	-15.5	-19.3	60.2	-3.8	0	-1.3
1029	CACCCCCTCCCCATCTTCTC SEQ ID NO:147	-15.5	-34	87.7	-18.5	0	-0.5
1036	CCACTCCCACCCCCTCCCCA SEQ ID NO:148	-15.5	-39.1	92.4	-23.6	0	0
1260	CCTTCAGATACAGGTAACCC SEQ ID NO:149	-15.5	-24.9	70.3	-9.4	0	-4
1781	ACAGTCCTGTTTGTGCTAAG SEQ ID NO:150	-15.5	-23.7	70.7	-8.2	0	-6.1
210	CAGCAGCCACAGTCGTCGAG SEQ ID NO:151	-15.4	-28	77.3	-12.6	0	-4.9
913	CTCTTTGGTTGACCTGTCTC SEQ ID NO:152	-15.4	-25.5	76.2	-10.1	0	-6.7
916	TCCCTCTTTGGTTGACCTGT SEQ ID NO:153	-15.4	-28.2	79.8	-12.8	0	-6.7
1530	CCTCAGATGTTTGAAAACCT SEQ ID NO:154	-15.4	-21.6	62.5	-5.7	-0.1	-5.7
918	GCTCCCTCTTTGGTTGACCT SEQ ID NO:155	-15.3	-29.7	82.9	-14.4	0	-6.7
330	TCACCAAAAGGATCCTCCCC SEQ ID NO:156	-15.2	-27.4	72.5	-11	-0.9	-9.9
538	TCTCACAATATTGCCATCTC SEQ ID NO:157	-15.2	-22.6	67.1	-6.9	0	-7.6
587	ATTTCCTCATTACGGGAGAC SEQ ID NO:158	-15.2	-23.2	67.5	-7.4	-0.3	-4.2
682	CTAGAAAGTTCCTAAAATGT SEQ ID NO:159	-15.2	-17.2	54	-2	0	-3.7
1347	GTAAAATACTTCTTAGATTT SEQ ID NO:160	-15.2	-15.6	51.7	0	0	-3.7
1600	GTTGCTCATTTTTTGACATT SEQ ID NO:161	-15.2	-21.2	65	-5.5	-0.2	-3.3
195	TCGAGCACTGTCCTCTTGCA SEQ ID NO:162	-15.1	-27.8	78.6	-11.1	-1.6	-6.3
319	ATCCTCCCCATTAGAAGGCT SEQ ID NO:163	-15.1	-28	76.5	-12.9	0	-3.7
394	GCAGGTCTCTCTGCAATCCA SEQ ID NO:164	-15.1	-27.7	79.7	-9.8	-2.8	-8.2
440	TCAGGCATTTTCCCGTCCCC SEQ ID NO:165	-15.1	-31.9	84	-16.3	-0.1	-4
779	TGGATGTTATGGATTGTAAG SEQ ID NO:166	-15.1	-18.9	58.9	-3.8	0	-2.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
780	ATGGATGTTATGGATTGTAA SEQ ID NO:167	-15.1	-18.9	58.7	-3.8	0	-2.2
1037	CCCACTCCCACCCCCTCCCC SEQ ID NO:168	-15.1	-40.4	94.4	-25.3	0	0
1780	CAGTCCTGTTTGTGCTAAGA SEQ ID NO:169	-15.1	-24.1	71.5	-9	0	-3.6
320	GATCCTCCCCATTAGAAGGC SEQ ID NO:170	-15	-27.7	75.9	-12.7	0	-3.5
365	TGCCGTAGGGACAGTCTTTG SEQ ID NO:171	-15	-26.1	74.5	-9.5	-1.5	-8.4
782	ATATGGATGTTATGGATTGT SEQ ID NO:172	-15	-19.6	60.8	-4.6	0	-1.8
249	CGGTAGCAAGTTTCTCCCCG SEQ ID NO:173	-14.9	-28.6	76.5	-13.7	0	-3.8
321	GGATCCTCCCCATTAGAAGG SEQ ID NO:174	-14.9	-27.1	74.2	-11.7	-0.1	-7.7
537	CTCACAATATTGCCATCTCC SEQ ID NO:175	-14.9	-24.2	69.2	-8.7	0	-8.5
1020	CCCATCTTCTCCTGCTCTTA SEQ ID NO:176	-14.9	-28.5	80.5	-13.6	0	-3.6
1261	TCCTTCAGATACAGGTAACC SEQ ID NO:177	-14.9	-23.3	68.2	-7.9	-0.1	-3.8
1279	TCCTATGCCCCAGAACCGTC SEQ ID NO:178	-14.9	-30	78.3	-15.1	0	-3
125	CCGCATAATTATTGCTCCAG SEQ ID NO:179	-14.8	-24	67	-7.9	-1.2	-8.4
768	GATTGTAAGTATCCTACTTT SEQ ID NO:180	-14.8	-20.1	62.2	-3.8	-1.4	-5.1
771	ATGGATTGTAAGTATCCTAC SEQ ID NO:181	-14.8	-20.2	62.1	-3.8	-1.6	-5.2
777	GATGTTATGGATTGTAAGTA SEQ ID NO:182	-14.8	-18.6	58.9	-3.8	0	-2.2
1649	TTGAAAATTCACCGAAGTCA SEQ ID NO:183	-14.8	-19	56.6	-4.2	0	-5.7
468	GTTACTGAATATTGGAAGAA SEQ ID NO:184	-14.7	-16.8	53.5	-2.1	0	-4.6
680	AGAAAGTTCCTAAAATGTTG SEQ ID NO:185	-14.7	-16.7	53	-2	0	-3.7
773	TTATGGATTGTAAGTATCCT SEQ ID NO:186	-14.7	-20.1	61.8	-3.8	-1.6	-5.2
920	TAGCTCCCTCTTTGGTTGAC SEQ ID NO:187	-14.7	-26.5	77	-11.8	0	-6.2
1271	CCCAGAACCGTCCTTCAGAT SEQ ID NO:188	-14.7	-27.9	74.6	-12.7	-0.2	-3.4
1281	TTTCCTATGCCCCAGAACCG SEQ ID NO:189	-14.7	-28.6	74.3	-13.9	0	-3
1418	ACTTGCACTAACACATTTAT SEQ ID NO:190	-14.7	-19.5	59.4	-4.8	0	-5
1609	GGTCCCTCTGTTGCTCATTT SEQ ID NO:191	-14.7	-28.3	81.9	-13.6	0	-3.6
481	GTTGGAAGACTTGGTTACTG SEQ ID NO:192	-14.6	-21.5	65.1	-6.9	0	-3.1
767	ATTGTAAGTATCCTACTTTT SEQ ID NO:193	-14.6	-19.6	61.2	-3.8	-1.1	-4.8
775	TGTTATGGATTGTAAGTATC SEQ ID NO:194	-14.6	-18.4	58.9	-3.8	0	-2.5
997	CTTCATTCCATATCCCAACA SEQ ID NO:195	-14.6	-24.3	68.4	-9.7	0	-2
1604	CTCTGTTGCTCATTTTTTGA SEQ ID NO:196	-14.6	-22.4	68.4	-7.8	0	-3.2

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1610	AGGTCCCTCTGTTGCTCATT SEQ ID NO:197	-14.6	-28.2	81.8	-13.6	0	-4
1642	TTCACCGAAGTCACAGCACT SEQ ID NO:198	-14.6	-24.9	70.3	-10.3	0	-4.1
1904	CATTCACAACTCTGTTGGCC SEQ ID NO:199	-14.6	-24.8	71.3	-8.4	-1.8	-7
2000	GTATCTTGTTCTTTTTTATT SEQ ID NO:200	-14.6	-19.2	62.2	-4.6	0	-0.9
933	CTTCAGCTTTGCCTAGCTCC SEQ ID NO:201	-14.5	-28.5	81.4	-12.6	-1.3	-7.8
1534	CATGCCTCAGATGTTTGAAA SEQ ID NO:202	-14.5	-21.7	63.6	-7.2	0	-3.3
1711	TTTCTGCTGAAAATTGATTC SEQ ID NO:203	-14.5	-17.9	56.2	-2.3	-1	-8.6
1791	ATCTAGTACAACAGTCCTGT SEQ ID NO:204	-14.5	-22.7	68.6	-8.2	0	-6.7
681	TAGAAAGTTCCTAAAATGTT SEQ ID NO:205	-14.4	-16.4	52.5	-2	0	-3.7
683	TCTAGAAAGTTCCTAAAATG SEQ ID NO:206	-14.4	-16.4	52.4	-2	0	-5.2
684	ATCTAGAAAGTTCCTAAAAT SEQ ID NO:207	-14.4	-16.4	52.5	-2	0	-6.2
766	TTGTAAGTATCCTACTTTTT SEQ ID NO:208	-14.4	-19.7	61.6	-3.8	-1.4	-5.1
911	CTTTGGTTGACCTGTCTCCA SEQ ID NO:209	-14.4	-26.9	77.2	-12	-0.2	-7.3
1034	ACTCCCACCCCCTCCCCATC SEQ ID NO:210	-14.4	-36.8	90.4	-22.4	0	-0.5
1533	ATGCCTCAGATGTTTGAAAA SEQ ID NO:211	-14.4	-20.3	60.4	-5.9	0	-3.6
1535	TCATGCCTCAGATGTTTGAA SEQ ID NO:212	-14.4	-22.8	67.2	-8.4	0	-4.4
1699	ATTGATTCTTCTTTTACAAA SEQ ID NO:213	-14.4	-17	54.8	-2.6	0	-3.5
209	AGCAGCCACAGTCGTCGAGC SEQ ID NO:214	-14.3	-29.1	80.6	-14.8	0	-4.9
445	GAATTTCAGGCATTTTCCCG SEQ ID NO:215	-14.3	-24.4	68.5	-9.6	-0.1	-4.6
470	TGGTTACTGAATATTGGAAG SEQ ID NO:216	-14.3	-18.1	56.5	-3.8	0	-4.6
486	AATCTGTTGGAAGACTTGGT SEQ ID NO:217	-14.3	-21.2	64	-6.9	0	-3.6
529	ATTGCCATCTCCAGATGCCA SEQ ID NO:218	-14.3	-28.1	77.2	-12.9	-0.7	-7.5
532	AATATTGCCATCTCCAGATG SEQ ID NO:219	-14.3	-22.6	65.5	-7.4	-0.8	-7.5
540	TCTCTCACAATATTGCCATC SEQ ID NO:220	-14.3	-22.6	67.1	-7.7	0	-8.5
765	TGTAAGTATCCTACTTTTTG SEQ ID NO:221	-14.3	-19.6	61.1	-3.8	-1.4	-5.1
772	TATGGATTGTAAGTATCCTA SEQ ID NO:222	-14.3	-19.7	60.9	-3.8	-1.6	-5.2
941	ACTGCGGTCTTCAGCTTTGC SEQ ID NO:223	-14.3	-27.3	78.7	-12.3	-0.5	-6
1031	CCCACCCCCTCCCCATCTTC SEQ ID NO:224	-14.3	-36.7	90.2	-22.4	0	-0.5
1422	GATGACTTGCACTAACACAT SEQ ID NO:225	-14.3	-20.8	61.7	-6.5	0	-5
1593	ATTTTTTGACATTTTTTGAA SEQ ID NO:226	-14.3	-16.4	53.3	-2.1	0	-2.4

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
1607	TCCCTCTGTTGCTCATTTTT SEQ ID NO:227	-14.3	-26.1	76.2	-11.8	0	-3.6
211	GCAGCAGCCACAGTCGTCGA SEQ ID NO:228	-14.2	-29.8	81.3	-14.6	-0.9	-5.2
392	AGGTCTCTCTGCAATCCATC SEQ ID NO:229	-14.2	-25.6	75.8	-11.4	0	-4.9
485	ATCTGTTGGAAGACTTGGTT SEQ ID NO:230	-14.2	-22	66.6	-6.9	-0.7	-3.6
776	ATGTTATGGATTGTAAGTAT SEQ ID NO:231	-14.2	-18	57.5	-3.8	0	-1.8
1705	CTGAAAATTGATTCTTCTTT SEQ ID NO:232	-14.2	-17.1	54.5	-2.3	-0.3	-4.9
1785	TACAACAGTCCTGTTTGTGC SEQ ID NO:233	-14.2	-23.7	70.2	-8.4	-1	-8.7
113	TGCTCCAGGCGGCCACCAGG SEQ ID NO:234	-14.1	-33.4	86.2	-17.7	-1.5	-10.2
234	CCCCGCCCTGCAGCGCACAC SEQ ID NO:235	-14.1	-36.2	87.1	-20.4	-1.7	-10.5
472	CTTGGTTACTGAATATTGGA SEQ ID NO:236	-14.1	-19.8	60.5	-5.7	0	-4.6
528	TTGCCATCTCCAGATGCCAT SEQ ID NO:237	-14.1	-28.1	77.2	-12.9	-1	-7.8
685	TATCTAGAAAGTTCCTAAAA SEQ ID NO:238	-14.1	-16.1	51.9	-2	0	-6.2
1650	ATTGAAAATTCACCGAAGTC SEQ ID NO:239	-14.1	-18.3	55.4	-4.2	0	-5.7
124	CGCATAATTATTGCTCCAGG SEQ ID NO:240	-14	-23.2	65.9	-7.9	-1.2	-8.4
480	TTGGAAGACTTGGTTACTGA SEQ ID NO:241	-14	-20.9	63.2	-6.9	0	-3.3
690	TGCTATATCTAGAAAGTTCC SEQ ID NO:242	-14	-20	61.5	-6	0	-6.2
871	ATTTTTAGTTCTTCAGTGTT SEQ ID NO:243	-14	-20.4	65.7	-6.4	0	-4.1
1641	TCACCGAAGTCACAGCACTT SEQ ID NO:244	-14	-24.9	70.3	-10.3	-0.3	-4.7
1648	TGAAAATTCACCGAAGTCAC SEQ ID NO:245	-14	-19.1	56.8	-5.1	0	-5.4
378	TCCATCCCGAAGGTGCCGTA SEQ ID NO:246	-13.9	-30.1	77.9	-14.9	-1.2	-6.2
484	TCTGTTGGAAGACTTGGTTA SEQ ID NO:247	-13.9	-21.7	66.1	-6.9	-0.7	-3.4
1268	AGAACCGTCCTTCAGATACA SEQ ID NO:248	-13.9	-23.8	67.7	-9.4	-0.2	-3.6
1345	AAAATACTTCTTAGATTTAT SEQ ID NO:249	-13.9	-14.4	48.9	0	-0.2	-3.8
1640	CACCGAAGTCACAGCACTTA SEQ ID NO:250	-13.9	-24.2	68.3	-10.3	0.1	-4.6
1698	TTGATTCTTCTTTTACAAAC SEQ ID NO:251	-13.9	-17.2	55.3	-3.3	0	-3
1713	GTTTTCTGCTGAAAATTGAT SEQ ID NO:252	-13.9	-18.7	57.8	-2.3	-2.5	-11.4
1714	TGTTTTCTGCTGAAAATTGA SEQ ID NO:253	-13.9	-18.7	57.7	-2.3	-2.5	-11.4
1782	AACAGTCCTGTTTGTGCTAA SEQ ID NO:254	-13.9	-23	68.1	-8.2	-0.7	-8.1
676	AGTTCCTAAAATGTTGGCTG SEQ ID NO:255	-13.8	-21.4	63.5	-7.6	0	-3.9
789	TTCAGTCATATGGATGTTAT SEQ ID NO:256	-13.8	-20	62.7	-5.5	-0.4	-6.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1010	CCTGCTCTTAAGTCTTCATT SEQ ID NO:257	-13.8	-23.8	71	-10	0	-6
1273	GCCCCAGAACCGTCCTTCAG SEQ ID NO:258	-13.8	-31.1	80.6	-16.8	-0.2	-3.4
1355	ACCAGTGGGTAAAATACTTC SEQ ID NO:259	-13.8	-20.6	61.6	-5.8	-0.9	-8.2
1536	ATCATGCCTCAGATGTTTGA SEQ ID NO:260	-13.8	-23.5	69.5	-9.7	0	-4.4
1611	AAGGTCCCTCTGTTGCTCAT SEQ ID NO:261	-13.8	-27.4	78.6	-13.6	0	-5.3
154	ACTGCTGTCACAGTGTTGAG SEQ ID NO:262	-13.7	-24.1	72.7	-9.1	-1.2	-6.4
204	CCACAGTCGTCGAGCACTGT SEQ ID NO:263	-13.7	-27.8	77	-12.2	-1.8	-11
236	CTCCCCGCCCTGCAGCGCAC SEQ ID NO:264	-13.7	-36.6	89.1	-21.4	-1.2	-10.5
366	GTGCCGTAGGGACAGTCTTT SEQ ID NO:265	-13.7	-27.3	78.3	-12	-1.5	-8.4
395	TGCAGGTCTCTCTGCAATCC SEQ ID NO:266	-13.7	-27	78.4	-9.8	-3.5	-9.5
482	TGTTGGAAGACTTGGTTACT SEQ ID NO:267	-13.7	-21.5	65.1	-6.9	-0.7	-3.8
483	CTGTTGGAAGACTTGGTTAC SEQ ID NO:268	-13.7	-21.5	65.1	-6.9	-0.7	-3.3
876	ATTGCATTTTTAGTTCTTCA SEQ ID NO:269	-13.7	-20.5	64.3	-6.8	0	-5.1
995	TCATTCCATATCCCAACATT SEQ ID NO:270	-13.7	-23.4	66.6	-9.7	0	-2
996	TTCATTCCATATCCCAACAT SEQ ID NO:271	-13.7	-23.4	66.6	-9.7	0	-2
1417	CTTGCACTAACACATTTATT SEQ ID NO:272	-13.7	-19.4	59.2	-5.7	0	-5
1790	TCTAGTACAACAGTCCTGTT SEQ ID NO:273	-13.7	-22.8	69	-8.2	-0.7	-8.1
1913	TTCCACACACATTCACAACT SEQ ID NO:274	-13.7	-22.4	64.9	-8.7	0	-1
188	CTGTCCTCTTGCAGCGCGGG SEQ ID NO:275	-13.6	-30.9	82.9	-16.4	-0.6	-9
325	AAAAGGATCCTCCCCATTAG SEQ ID NO:276	-13.6	-23.9	66.3	-9.1	-0.9	-9.9
675	GTTCCTAAAATGTTGGCTGT SEQ ID NO:277	-13.6	-22.6	66.4	-9	0	-3.9
758	ATCCTACTTTTTGTTTTCTG SEQ ID NO:278	-13.6	-21.3	65.7	-7.7	0	-2.2
788	TCAGTCATATGGATGTTATG SEQ ID NO:279	-13.6	-19.9	62.2	-6.3	0.2	-6.7
1275	ATGCCCCAGAACCGTCCTTC SEQ ID NO:280	-13.6	-30.4	79.1	-16.8	0	-3
1346	TAAAATACTTCTTAGATTTA SEQ ID NO:281	-13.6	-14.1	48.4	0	-0.2	-3.8
1647	GAAAATTCACCGAAGTCACA SEQ ID NO:282	-13.6	-19.8	58	-6.2	0	-4.1
1786	GTACAACAGTCCTGTTTGTG SEQ ID NO:283	-13.6	-23.1	69.2	-8.4	-1	-8.7
123	GCATAATTATTGCTCCAGGC SEQ ID NO:284	-13.5	-24.2	69.9	-9.8	-0.7	-8.1
379	ATCCATCCCGAAGGTGCCGT SEQ ID NO:285	-13.5	-30.4	78.4	-15.6	-1.2	-6.2
783	CATATGGATGTTATGGATTG SEQ ID NO:286	-13.5	-19.1	58.9	-5.6	0	-5.2

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1041	ATTTCCCACTCCCACCCCCT SEQ ID NO:287	-13.5	-34.6	86.4	-21.1	0	-0.3
1612	TAAGGTCCCTCTGTTGCTCA SEQ ID NO:288	-13.5	-27.1	78.1	-13.6	0	-4.7
1978	ACAATAATAAACATGTCCTT SEQ ID NO:289	-13.5	-17	53.1	-3.5	0	-6.9
471	TTGGTTACTGAATATTGGAA SEQ ID NO:290	-13.4	-18.2	56.7	-4.8	0	-4.6
542	CTTCTCTCACAATATTGCCA SEQ ID NO:291	-13.4	-23.2	67.9	-9.2	0	-8.5
686	ATATCTAGAAAGTTCCTAAA SEQ ID NO:292	-13.4	-16.8	53.7	-3.4	0	-6.2
873	GCATTTTTAGTTCTTCAGTG SEQ ID NO:293	-13.4	-21.6	67.7	-8.2	0	-3.5
907	GGTTGACCTGTCTCCATGTA SEQ ID NO:294	-13.4	-26.7	77.4	-13.3	0	-5.9
1423	AGATGACTTGCACTAACACA SEQ ID NO:295	-13.4	-20.8	62	-7.4	0	-5
1427	GGGAAGATGACTTGCACTAA SEQ ID NO:296	-13.4	-21.3	62.7	-7	-0.7	-5.3
1601	TGTTGCTCATTTTTTGACAT SEQ ID NO:297	-13.4	-21.1	64.5	-7.2	-0.2	-3.6
1704	TGAAAATTGATTCTTCTTTT SEQ ID NO:298	-13.4	-16.3	52.9	-2.3	-0.3	-4.9
1784	ACAACAGTCCTGTTTGTGCT SEQ ID NO:299	-13.4	-24.9	72.8	-10.5	-0.9	-8.4
1902	TTCACAACTCTGTTGGCCAA SEQ ID NO:300	-13.4	-24.1	69	-8.8	-1.8	-10.8
1977	CAATAATAAACATGTCCTTT SEQ ID NO:301	-13.4	-16.9	52.9	-3.5	0	-6.9
792	GTGTTCAGTCATATGGATGT SEQ ID NO:302	-13.3	-22.6	69.8	-8.6	-0.4	-6.1
870	TTTTTAGTTCTTCAGTGTTA SEQ ID NO:303	-13.3	-20.1	65.1	-6.8	0	-4.1
935	GTCTTCAGCTTTGCCTAGCT SEQ ID NO:304	-13.3	-27.7	81.6	-13.1	-1.2	-7.7
1038	TCCCACTCCCACCCCCTCCC SEQ ID NO:305	-13.3	-38.8	93.4	-25.5	0	0
1712	TTTTCTGCTGAAAATTGATT SEQ ID NO:306	-13.3	-17.6	55.2	-2.3	-2	-10.6
1715	ATGTTTTCTGCTGAAAATTG SEQ ID NO:307	-13.3	-18.1	56.5	-2.3	-2.5	-11.4
1789	CTAGTACAACAGTCCTGTTT SEQ ID NO:308	-13.3	-22.5	67.8	-8.2	-0.9	-8.4
478	GGAAGACTTGGTTACTGAAT SEQ ID NO:309	-13.2	-20.1	60.9	-6.9	0	-3.1
479	TGGAAGACTTGGTTACTGAA SEQ ID NO:310	-13.2	-20.1	60.8	-6.9	0	-3.1
531	ATATTGCCATCTCCAGATGC SEQ ID NO:311	-13.2	-25.1	72	-10.8	-1	-7.8
908	TGGTTGACCTGTCTCCATGT SEQ ID NO:312	-13.2	-27	77.8	-13.3	-0.2	-7.2
1792	CATCTAGTACAACAGTCCTG SEQ ID NO:313	-13.2	-22.2	66.5	-9	0	-5.3
126	ACCGCATAATTATTGCTCCA SEQ ID NO:314	-13.1	-24.2	67.3	-9.8	-1.2	-8.4
687	TATATCTAGAAAGTTCCTAA SEQ ID NO:315	-13.1	-17.2	54.9	-4.1	0	-6.2
1497	GTTTTTATTCTAACCATTTT SEQ ID NO:316	-13.1	-18.9	59.2	-5.8	0	-2.3

position	oligo	kcal/ mol total binding	kcal/ mol duplex form-ation	deg C Tm of Duplex	kcal/ mol target struc-ture	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1542	AAATTTATCATGCCTCAGAT SEQ ID NO:317	-13.1	-20	60.2	-6.9	0	-4.6
1592	TTTTTTGACATTTTTTGAAA SEQ ID NO:318	-13.1	-15.7	51.6	-2.1	-0.1	-2.5
1779	AGTCCTGTTTGTGCTAAGAT SEQ ID NO:319	-13.1	-23.4	70.3	-10.3	0	-3.6
114	TTGCTCCAGGCGGCCACCAG SEQ ID NO:320	-13	-32.3	84.2	-17.7	-1.4	-10.2
115	ATTGCTCCAGGCGGCCACCA SEQ ID NO:321	-13	-32.3	83.8	-17.7	-1.4	-10.2
324	AAAGGATCCTCCCCATTAGA SEQ ID NO:322	-13	-25.2	69.6	-11	-0.9	-9.9
541	TTCTCTCACAATATTGCCAT SEQ ID NO:323	-13	-22.3	65.9	-8.7	0	-8.5
1019	CCATCTTCTCCTGCTCTTAA SEQ ID NO:324	-13	-25.8	74.3	-12.8	0	-3.6
1342	ATACTTCTTAGATTTATCTC SEQ ID NO:325	-13	-18.2	59.3	-4.3	-0.7	-5.1
1358	ACCACCAGTGGGTAAAATAC SEQ ID NO:326	-13	-22.1	63.4	-7.8	-1.2	-9
111	CTCCAGGCGGCCACCAGGTG SEQ ID NO:327	-12.9	-32.8	85.5	-19	-0.4	-9.4
155	CACTGCTGTCACAGTGTTGA SEQ ID NO:328	-12.9	-24.8	73.6	-9.1	-2.8	-8.5
391	GGTCTCTCTGCAATCCATCC SEQ ID NO:329	-12.9	-27.6	79.2	-14.7	0	-4.9
688	CTATATCTAGAAAGTTCCTA SEQ ID NO:330	-12.9	-18.8	58.8	-5.9	0	-5.7
872	CATTTTTAGTTCTTCAGTGT SEQ ID NO:331	-12.9	-21	66.6	-8.1	0	-4.1
1186	CTCAAATTTCCATAAGCTTC SEQ ID NO:332	-12.9	-20.1	60.7	-7.2	0	-6.8
1276	TATGCCCCAGAACCGTCCTT SEQ ID NO:333	-12.9	-29.7	77	-16.8	0	-3
1282	GTTTCCTATGCCCCAGAACC SEQ ID NO:334	-12.9	-29	77.7	-16.1	0	-3
1540	ATTTATCATGCCTCAGATGT SEQ ID NO:335	-12.9	-22.6	67.6	-9.7	0	-4.4
112	GCTCCAGGCGGCCACCAGGT SEQ ID NO:336	-12.8	-34.6	90	-20.4	-1.1	-10.2
212	GGCAGCAGCCACAGTCGTCG SEQ ID NO:337	-12.8	-30.4	82.5	-14.9	-2.7	-9.6
439	CAGGCATTTTCCCGTCCCCC SEQ ID NO:338	-12.8	-33.5	85.4	-20.2	-0.1	-4
790	GTTCAGTCATATGGATGTTA SEQ ID NO:339	-12.8	-21.2	66.1	-7.7	-0.4	-6.7
795	CAAGTGTTCAGTCATATGGA SEQ ID NO:340	-12.8	-21.4	65.6	-8.6	0	-6.2
994	CATTCCATATCCCAACATTA SEQ ID NO:341	-12.8	-22.7	64.6	-9.9	0	-2
1431	GGTAGGGAAGATGACTTGCA SEQ ID NO:342	-12.8	-23.3	68.4	-9.6	-0.7	-5.9
1543	TAAATTTATCATGCCTCAGA SEQ ID NO:343	-12.8	-19.7	59.7	-6.9	0	-5.5
1590	TTTTGACATTTTTTGAAATC SEQ ID NO:344	-12.8	-15.9	52.1	-2.1	-0.9	-3.8
1976	AATAATAAACATGTCCTTTT SEQ ID NO:345	-12.8	-16.3	52	-3.5	0	-6.9
322	AGGATCCTCCCCATTAGAAG SEQ ID NO:346	-12.7	-25.9	72	-12.1	-0.9	-9.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
738	GATCCACCATGCATCACAAT SEQ ID NO:347	-12.7	-24.4	68.2	-11.7	0	-6.6
785	GTCATATGGATGTTATGGAT SEQ ID NO:348	-12.7	-20.6	63.3	-7.2	-0.4	-6.2
942	CACTGCGGTCTTCAGCTTTG SEQ ID NO:349	-12.7	-26.2	75.3	-12.8	-0.5	-6.2
1187	ACTCAAATTTCCATAAGCTT SEQ ID NO:350	-12.7	-19.9	59.8	-7.2	0	-6.4
1278	CCTATGCCCCAGAACCGTCC SEQ ID NO:351	-12.7	-31.6	79.8	-18.9	0	-2.6
1428	AGGGAAGATGACTTGCACTA SEQ ID NO:352	-12.7	-22	65.1	-8.4	-0.7	-5.3
1979	AACAATAATAAACATGTCCT SEQ ID NO:353	-12.7	-16.2	51.2	-3.5	0	-6.9
735	CCACCATGCATCACAATTTG SEQ ID NO:354	-12.6	-23.6	66.1	-11	0	-6.4
761	AGTATCCTACTTTTTGTTTT SEQ ID NO:355	-12.6	-20.9	65.2	-7.8	-0.2	-2.9
992	TTCCATATCCCAACATTAAT SEQ ID NO:356	-12.6	-21.3	61.5	-8.7	0	-3.8
993	ATTCCATATCCCAACATTAA SEQ ID NO:357	-12.6	-21.3	61.5	-8.7	0	-2.6
1127	TTTTGACTTTTCCCAAAGCC SEQ ID NO:358	-12.6	-23.8	67.4	-9.8	-1.3	-6.3
1277	CTATGCCCCAGAACCGTCCT SEQ ID NO:359	-12.6	-30.5	78.4	-17.9	0	-3
1591	TTTTTGACATTTTTTGAAAT SEQ ID NO:360	-12.6	-15.6	51.3	-2.1	-0.7	-3.1
1594	CATTTTTTGACATTTTTTGA SEQ ID NO:361	-12.6	-17.8	56.5	-5.2	0	-2.4
1778	GTCCTGTTTGTGCTAAGATT SEQ ID NO:362	-12.6	-23.5	70.4	-10.9	0	-3.6
1975	ATAATAAACATGTCCTTTTA SEQ ID NO:363	-12.6	-16.7	53.2	-4.1	0	-6.9
15	GTGGTCTTTGCTGGTGGGAA SEQ ID NO:364	-12.5	-26.5	77.3	-14	0	-3.6
331	TTCACCAAAAGGATCCTCCC SEQ ID NO:365	-12.5	-25.5	69.6	-11.8	-0.9	-9.9
473	ACTTGGTTACTGAATATTGG SEQ ID NO:366	-12.5	-19.4	59.8	-6.9	0	-4.6
536	TCACAATATTGCCATCTCCA SEQ ID NO:367	-12.5	-24	68.5	-10.9	0	-8.5
578	TTACGGGAGACCCGGCAGCA SEQ ID NO:368	-12.5	-29.6	77.1	-13.4	-3.7	-12.1
1341	TACTTCTTAGATTTATCTCT SEQ ID NO:369	-12.5	-19.1	61.4	-5.7	-0.7	-5.1
1528	TCAGATGTTTGAAAACCTTA SEQ ID NO:370	-12.5	-18.5	56.9	-5.5	-0.1	-5.7
1696	GATTCTTCTTTTACAAACCT SEQ ID NO:371	-12.5	-20	60.8	-7.5	0	-1.9
1697	TGATTCTTCTTTTACAAACC SEQ ID NO:372	-12.5	-19.1	58.8	-6.6	0	-2.6
377	CCATCCCGAAGGTGCCGTAG SEQ ID NO:373	-12.4	-29.7	76.7	-16.4	-0.7	-6.2
588	CATTTCCTCATTACGGGAGA SEQ ID NO:374	-12.4	-23.7	68	-10.7	-0.3	-4.2
796	ACAAGTGTTCAGTCATATGG SEQ ID NO:375	-12.4	-21	64.7	-8.6	0	-6.2
875	TTGCATTTTTAGTTCTTCAG SEQ ID NO:376	-12.4	-20.5	64.6	-8.1	0	-5.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1426	GGAAGATGACTTGCACTAAC SEQ ID NO:377	-12.4	-20.3	60.8	-7	-0.7	-5.3
1595	TCATTTTTTGACATTTTTTG SEQ ID NO:378	-12.4	-17.6	56.5	-5.2	0	-2.5
1905	ACATTCACAACTCTGTTGGC SEQ ID NO:379	-12.4	-23	68.2	-8.8	-1.8	-7
1980	GAACAATAATAAACATGTCC SEQ ID NO:380	-12.4	-15.9	50.6	-3.5	0	-6.9
760	GTATCCTACTTTTTGTTTTC SEQ ID NO:381	-12.3	-21.3	66.6	-9	0	-2.2
763	TAAGTATCCTACTTTTTGTT SEQ ID NO:382	-12.3	-19.7	61.6	-5.9	-1.4	-5.1
793	AGTGTTCAGTCATATGGATG SEQ ID NO:383	-12.3	-21.4	66.5	-8.6	-0.1	-6.4
1011	TCCTGCTCTTAAGTCTTCAT SEQ ID NO:384	-12.3	-24.1	72.3	-11.8	0	-6
1042	TATTTCCCACTCCCACCCCC SEQ ID NO:385	-12.3	-33.4	84.2	-21.1	0	-0.7
1147	GGGGTTTTCTGGTTGTTTTA SEQ ID NO:386	-12.3	-24.1	73.6	-11.8	0	-1.9
1188	TACTCAAATTTCCATAAGCT SEQ ID NO:387	-12.3	-19.5	59	-7.2	0	-4.8
1269	CAGAACCGTCCTTCAGATAC SEQ ID NO:388	-12.3	-23.8	67.7	-11	-0.2	-3.4
1496	TTTTTATTCTAACCATTTTC SEQ ID NO:389	-12.3	-18.1	57.5	-5.8	0	-1.4
1783	CAACAGTCCTGTTTGTGCTA SEQ ID NO:390	-12.3	-24.4	71.6	-11.1	-0.9	-8.4
229	CCCTGCAGCGCACACTCGGC SEQ ID NO:391	-12.2	-32.7	83.8	-19.6	-0.7	-8.5
323	AAGGATCCTCCCCATTAGAA SEQ ID NO:392	-12.2	-25.2	69.6	-11.8	-0.9	-9.9
633	GAGCCTTCTCTCAGAAATCA SEQ ID NO:393	-12.2	-23.4	69	-10.3	-0.7	-5.1
801	CACATACAAGTGTTCAGTCA SEQ ID NO:394	-12.2	-21.4	65.3	-8.6	-0.3	-4.1
864	GTTCTTCAGTGTTACTATAC SEQ ID NO:395	-12.2	-20.7	66	-8.5	0	-4.1
869	TTTTAGTTCTTCAGTGTTAC SEQ ID NO:396	-12.2	-20.2	65.3	-8	0	-4.1
990	CCATATCCCAACATTAATGT SEQ ID NO:397	-12.2	-22	62.7	-8.7	0	-10.2
1009	CTGCTCTTAAGTCTTCATTC SEQ ID NO:398	-12.2	-22.2	68.8	-10	0	-5.4
1221	TTTTGAAATTGCTCTCAGTT SEQ ID NO:399	-12.2	-20	61.8	-7.8	0	-3.6
1544	ATAAATTTATCATGCCTCAG SEQ ID NO:400	-12.2	-19.1	58.4	-6.9	0	-7.3
1703	GAAAATTGATTCTTCTTTTA SEQ ID NO:401	-12.2	-16	52.4	-3.8	0	-4.1
1906	CACATTCACAACTCTGTTGG SEQ ID NO:402	-12.2	-21.9	65.1	-7.9	-1.8	-7
156	TCACTGCTGTCACAGTGTTG SEQ ID NO:403	-12.1	-24.6	74	-9.1	-3.4	-9.7
689	GCTATATCTAGAAAGTTCCT SEQ ID NO:404	-12.1	-20.9	63.6	-8.8	0	-6.2
794	AAGTGTTCAGTCATATGGAT SEQ ID NO:405	-12.1	-20.7	64.3	-8.6	0	-6.2
868	TTTAGTTCTTCAGTGTTACT SEQ ID NO:406	-12.1	-21	67.1	-8.9	0	-4.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
984	CCCAACATTAATGTACATCA SEQ ID NO:407	-12.1	-20.9	60.8	-7.5	-0.2	-10.5
985	TCCCAACATTAATGTACATC SEQ ID NO:408	-12.1	-20.6	61	-7.5	0.3	-10
1133	GTTTTATTTTGACTTTTCCC SEQ ID NO:409	-12.1	-21.9	66.2	-9.8	0	-2
1344	AAATACTTCTTAGATTTATC SEQ ID NO:410	-12.1	-15.5	51.8	-3.4	0	-3.1
1357	CCACCAGTGGGTAAAATACT SEQ ID NO:411	-12.1	-22.8	64.6	-9.5	-1.1	-8.2
1359	AACCACCAGTGGGTAAAATA SEQ ID NO:412	-12.1	-21.2	60.9	-7.8	-1.2	-9
1506	GAGTCATAGGTTTTTATTCT SEQ ID NO:413	-12.1	-20.5	65.2	-8.4	0	-4.1
1526	AGATGTTTGAAAACCTTATA SEQ ID NO:414	-12.1	-17.1	53.9	-4.5	-0.1	-5.7
1608	GTCCCTCTGTTGCTCATTTT SEQ ID NO:415	-12.1	-27.2	79.5	-15.1	0	-3.6
1651	AATTGAAAATTCACCGAAGT SEQ ID NO:416	-12.1	-17.2	52.7	-4.2	-0.7	-5.7
1793	ACATCTAGTACAACAGTCCT SEQ ID NO:417	-12.1	-22.4	67.2	-10.3	0	-5.3
116	TATTGCTCCAGGCGGCCACC SEQ ID NO:418	-12	-31.3	82.3	-17.7	-1.4	-10.2
301	CTGACACCTCAGCCCCGGGC SEQ ID NO:419	-12	-33.4	85.2	-18.8	-1.4	-13.3
535	CACAATATTGCCATCTCCAG SEQ ID NO:420	-12	-23.6	67.2	-11	0	-8.5
691	ATGCTATATCTAGAAAGTTC SEQ ID NO:421	-12	-18	57.6	-6	0	-6.2
762	AAGTATCCTACTTTTTGTTT SEQ ID NO:422	-12	-20.1	62.5	-6.9	-1.1	-4.7
865	AGTTCTTCAGTGTTACTATA SEQ ID NO:423	-12	-20.5	65.6	-8.5	0	-4.1
866	TAGTTCTTCAGTGTTACTAT SEQ ID NO:424	-12	-20.5	65.6	-8.5	0	-4.1
991	TCCATATCCCAACATTAATG SEQ ID NO:425	-12	-21.2	61.1	-8.7	0	-8.2
1035	CACTCCCACCCCCTCCCCAT SEQ ID NO:426	-12	-37.1	89.5	-25.1	0	-0.3
1146	GGGTTTTCTGGTTGTTTTAT SEQ ID NO:427	-12	-22.9	70.6	-10.9	0	-1.5
1218	TGAAATTGCTCTCAGTTCAA SEQ ID NO:428	-12	-20.1	61.3	-7.4	-0.4	-4.9
1846	TCTTAAATAAGTTCTTCACT SEQ ID NO:429	-12	-17.6	56.4	-5.6	0	-4.9
153	CTGCTGTCACAGTGTTGAGG SEQ ID NO:430	-11.9	-25.1	74.9	-12.5	-0.4	-6
367	GGTGCCGTAGGGACAGTCTT SEQ ID NO:431	-11.9	-28.4	80.6	-14.9	-1.5	-8.4
475	AGACTTGGTTACTGAATATT SEQ ID NO:432	-11.9	-18.8	58.8	-6.9	0	-4.6
632	AGCCTTCTCTCAGAAATCAC SEQ ID NO:433	-11.9	-23	68.2	-10.3	-0.6	-5.1
909	TTGGTTGACCTGTCTCCATG SEQ ID NO:434	-11.9	-25.9	74.6	-13.3	-0.4	-7.6
1193	TTTGTTACTCAAATTTCCAT SEQ ID NO:435	-11.9	-19.3	59.3	-6.2	-1.1	-4.5
1425	GAAGATGACTTGCACTAACA SEQ ID NO:436	-11.9	-19.8	59.5	-7	-0.7	-5.3

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1541	AATTTATCATGCCTCAGATG SEQ ID NO:437	-11.9	-20.7	62.2	-8.8	0	-4.4
1912	TCCACACACATTCACAACTC SEQ ID NO:438	-11.9	-22.7	66	-10.8	0	-1
390	GTCTCTCTGCAATCCATCCC SEQ ID NO:439	-11.8	-28.4	80.1	-16.6	0	-4.9
467	TTACTGAATATTGGAAGAAG SEQ ID NO:440	-11.8	-15.6	50.9	-3.8	0	-4.6
579	ATTACGGGAGACCCGGCAGC SEQ ID NO:441	-11.8	-28.9	76.1	-13.4	-3.7	-11
784	TCATATGGATGTTATGGATT SEQ ID NO:442	-11.8	-19.5	60.4	-7	-0.4	-6.2
910	TTTGGTTGACCTGTCTCCAT SEQ ID NO:443	-11.8	-26	75.2	-13.5	-0.4	-7.6
1220	TTTGAAATTGCTCTCAGTTC SEQ ID NO:444	-11.8	-20.3	62.9	-8.5	0	-3.9
1430	GTAGGGAAGATGACTTGCAC SEQ ID NO:445	-11.8	-22.3	66.3	-9.6	-0.7	-5.3
1495	TTTTATTCTAACCATTTTCA SEQ ID NO:446	-11.8	-18.7	58.4	-6.9	0	-1.4
1501	ATAGGTTTTTATTCTAACCA SEQ ID NO:447	-11.8	-19.5	60.4	-5.5	-2.2	-5.9
302	GCTGACACCTCAGCCCCGGG SEQ ID NO:448	-11.7	-33.4	85.2	-16.7	-3.5	-18.2
398	AGTTGCAGGTCTCTCTGCAA SEQ ID NO:449	-11.7	-25.9	77.3	-9.5	-4.7	-12
435	CATTTTCCCGTCCCCCTGTC SEQ ID NO:450	-11.7	-32.3	84.3	-20.6	0	-2.6
477	GAAGACTTGGTTACTGAATA SEQ ID NO:451	-11.7	-18.6	57.8	-6.9	0	-3.1
527	TGCCATCTCCAGATGCCATG SEQ ID NO:452	-11.7	-28	76.7	-15.2	-1	-7.8
543	TCTTCTCTCACAATATTGCC SEQ ID NO:453	-11.7	-22.9	68.3	-10.6	0	-8.5
943	TCACTGCGGTCTTCAGCTTT SEQ ID NO:454	-11.7	-26.6	77.3	-14.2	-0.4	-6.2
1219	TTGAAATTGCTCTCAGTTCA SEQ ID NO:455	-11.7	-20.9	63.8	-8.5	-0.4	-5
1259	CTTCAGATACAGGTAACCCG SEQ ID NO:456	-11.7	-23.7	66.9	-11	-0.9	-4.5
1274	TGCCCCAGAACCGTCCTTCA SEQ ID NO:457	-11.7	-31.1	80.1	-18.9	-0.2	-3.4
1356	CACCAGTGGGTAAAATACTT SEQ ID NO:458	-11.7	-20.9	61.4	-8	-1.1	-8.2
1360	AAACCACCAGTGGGTAAAAT SEQ ID NO:459	-11.7	-20.8	59.6	-7.8	-1.2	-9
1639	ACCGAAGTCACAGCACTTAT SEQ ID NO:460	-11.7	-23.5	67.1	-11.1	-0.5	-4.6
1787	AGTACAACAGTCCTGTTTGT SEQ ID NO:461	-11.7	-23.1	69.6	-10.5	-0.8	-8.3
110	TCCAGGCGGCCACCAGGTGT SEQ ID NO:462	-11.6	-33.1	87.1	-19.9	-1.4	-10.2
160	GCACTCACTGCTGTCACAGT SEQ ID NO:463	-11.6	-26.9	78.8	-14	-1.2	-6.3
187	TGTCCTCTTGCAGCGCGGGC SEQ ID NO:464	-11.6	-31.8	85.4	-19.3	-0.6	-9.1
250	GCGGTAGCAAGTTTCTCCCC SEQ ID NO:465	-11.6	-29.6	81	-17	-0.9	-4.5
799	CATACAAGTGTTCAGTCATA SEQ ID NO:466	-11.6	-20.2	62.8	-8.6	0	-3.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
800	ACATACAAGTGTTCAGTCAT SEQ ID NO:467	-11.6	-20.7	64	-8.6	-0.1	-3.7
903	GACCTGTCTCCATGTAAGAT SEQ ID NO:468	-11.6	-24.1	70.1	-12.5	0	-5.5
904	TGACCTGTCTCCATGTAAGA SEQ ID NO:469	-11.6	-24.1	70	-12.5	0	-5.3
1012	CTCCTGCTCTTAAGTCTTCA SEQ ID NO:470	-11.6	-25	74.5	-13.4	0	-6
1132	TTTTATTTTGACTTTTCCCA SEQ ID NO:471	-11.6	-21.4	64.2	-9.8	0	-1.7
1204	GTTCAAAGCTGTTTGTTACT SEQ ID NO:472	-11.6	-21.2	65.1	-8.1	-1.4	-6
1500	TAGGTTTTTATTCTAACCAT SEQ ID NO:473	-11.6	-19.5	60.4	-5.7	-2.2	-5.9
1911	CCACACACATTCACAACTCT SEQ ID NO:474	-11.6	-23.2	66.4	-11.6	0	-1
127	CACCGCATAATTATTGCTCC SEQ ID NO:475	-11.5	-24.2	67.3	-11.4	-1.2	-8.4
205	GCCACAGTCGTCGAGCACTG SEQ ID NO:476	-11.5	-28.4	77.9	-15.6	-1.1	-9.6
352	GTCTTTGCAGATACCAAACT SEQ ID NO:477	-11.5	-22.1	64.9	-10	-0.3	-4.9
397	GTTGCAGGTCTCTCTGCAAT SEQ ID NO:478	-11.5	-25.9	76.9	-9.5	-4.9	-12.2
487	AAATCTGTTGGAAGACTTGG SEQ ID NO:479	-11.5	-19.3	58.9	-6.9	-0.7	-3.6
1145	GGTTTTCTGGTTGTTTTATT SEQ ID NO:480	-11.5	-21.8	68.2	-10.3	0	-1.5
1416	TTGCACTAACACATTTATTT SEQ ID NO:481	-11.5	-18.6	57.6	-7.1	0	-5
1429	TAGGGAAGATGACTTGCACT SEQ ID NO:482	-11.5	-22	65.1	-10	-0.1	-5
1529	CTCAGATGTTTGAAAACCTT SEQ ID NO:483	-11.5	-19.7	59.3	-7.7	-0.1	-5.7
228	CCTGCAGCGCACACTCGGCA SEQ ID NO:484	-11.4	-31.4	81.5	-19.1	-0.7	-8.8
233	CCCGCCCTGCAGCGCACACT SEQ ID NO:485	-11.4	-35.1	85.8	-22	-1.7	-10.5
568	CCCGGCAGCATTCTCTTTCA SEQ ID NO:486	-11.4	-29	79.5	-17.6	0	-6.3
577	TACGGGAGACCCGGCAGCAT SEQ ID NO:487	-11.4	-29.5	76.7	-14.4	-3.7	-12.1
877	AATTGCATTTTTAGTTCTTC SEQ ID NO:488	-11.4	-19.1	60.7	-7.7	0	-5.1
1039	TTCCCACTCCCACCCCCTCC SEQ ID NO:489	-11.4	-36.9	90.9	-25.5	0	0
1202	TCAAAGCTGTTTGTTACTCA SEQ ID NO:490	-11.4	-21	64.2	-8.1	-1.4	-6
1515	AACCTTATAGAGTCATAGGT SEQ ID NO:491	-11.4	-20.9	64	-8.6	-0.8	-6.3
1602	CTGTTGCTCATTTTTTGACA SEQ ID NO:492	-11.4	-22	66.5	-10.1	-0.1	-3.6
266	CCATGCCTGAGACTGTGCGG SEQ ID NO:493	-11.3	-28.7	77	-16.8	-0.3	-4.2
317	CCTCCCCATTAGAAGGCTGA SEQ ID NO:494	-11.3	-28.2	76	-16.9	0	-3.7
530	TATTGCCATCTCCAGATGCC SEQ ID NO:495	-11.3	-27.1	75.6	-14.7	-1	-7.8
692	TATGCTATATCTAGAAAGTT SEQ ID NO:496	-11.3	-17.3	55.6	-6	0	-6.2

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
693	TTATGCTATATCTAGAAAGT SEQ ID NO:497	-11.3	-17.3	55.6	-6	0	-6.2
759	TATCCTACTTTTTGTTTTCT SEQ ID NO:498	-11.3	-21	65.2	-9.7	0	-2.2
787	CAGTCATATGGATGTTATGG SEQ ID NO:499	-11.3	-20.7	63.4	-8.7	-0.4	-6.2
874	TGCATTTTTAGTTCTTCAGT SEQ ID NO:500	-11.3	-21.6	67.7	-10.3	0	-4.7
1413	CACTAACACATTTATTTATA SEQ ID NO:501	-11.3	-16.1	52.3	-4.8	0	-1.7
1527	CAGATGTTTGAAAACCTTAT SEQ ID NO:502	-11.3	-18.1	55.6	-6.8	0.6	-5
1589	TTTGACATTTTTTGAAATCC SEQ ID NO:503	-11.3	-17.8	55.6	-5.5	-0.9	-3.8
1907	ACACATTCACAACTCTGTTG SEQ ID NO:504	-11.3	-20.9	63.1	-8.1	-1.4	-6.5
118	ATTATTGCTCCAGGCGGCCA SEQ ID NO:505	-11.2	-29.2	78.7	-16.4	-1.4	-10.2
332	CTTCACCAAAAGGATCCTCC SEQ ID NO:506	-11.2	-24.4	68	-12.1	-0.5	-9.9
489	ACAAATCTGTTGGAAGACTT SEQ ID NO:507	-11.2	-19	58.2	-6.9	-0.8	-4.4
631	GCCTTCTCTCAGAAATCACA SEQ ID NO:508	-11.2	-23.7	69.1	-11.7	-0.6	-4.6
1192	TTGTTACTCAAATTTCCATA SEQ ID NO:509	-11.2	-18.9	58.4	-7.2	-0.1	-4.5
1194	GTTTGTTACTCAAATTTCCA SEQ ID NO:510	-11.2	-20.5	62.4	-7.7	-1.6	-4.6
1343	AATACTTCTTAGATTTATCT SEQ ID NO:511	-11.2	-17.1	55.8	-5.2	-0.5	-4.7
1644	AATTCACCGAAGTCACAGCA SEQ ID NO:512	-11.2	-23.1	65.7	-11.9	0	-4.1
1847	TTCTTAAATAAGTTCTTCAC SEQ ID NO:513	-11.2	-16.8	54.8	-5.6	0	-4.9
1908	CACACATTCACAACTCTGTT SEQ ID NO:514	-11.2	-21.6	64.4	-9.9	-0.2	-3.1
267	TCCATGCCTGAGACTGTGCG SEQ ID NO:515	-11.1	-27.9	76.2	-16.8	0.4	-4.2
318	TCCTCCCCATTAGAAGGCTG SEQ ID NO:516	-11.1	-28	76.3	-16.9	0	-3.7
446	GGAATTTCAGGCATTTTCCC SEQ ID NO:517	-11.1	-24.8	71	-13	-0.4	-5
476	AAGACTTGGTTACTGAATAT SEQ ID NO:518	-11.1	-18	56.5	-6.9	0	-3.1
589	CCATTTCCTCATTACGGGAG SEQ ID NO:519	-11.1	-25.1	70.3	-14	0	-4.2
906	GTTGACCTGTCTCCATGTAA SEQ ID NO:520	-11.1	-24.8	72.1	-13.7	0	-5.1
1008	TGCTCTTAAGTCTTCATTCC SEQ ID NO:521	-11.1	-23.3	70.6	-12.2	0	-6
1237	AACTACATCAGCAGCCTTTT SEQ ID NO:522	-11.1	-23.6	68.7	-12.5	0	-4.5
1256	CAGATACAGGTAACCCGGGA SEQ ID NO:523	-11.1	-25.3	69.3	-12.7	-0.9	-10.7
1257	TCAGATACAGGTAACCCGGG SEQ ID NO:524	-11.1	-25.1	69.6	-12.7	-0.9	-10.2
1499	AGGTTTTTATTCTAACCATT SEQ ID NO:525	-11.1	-19.9	61.3	-6.6	-2.2	-5.9
1512	CTTATAGAGTCATAGGTTTT SEQ ID NO:526	-11.1	-19.7	62.7	-8.6	0	-4.8

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1841	AATAAGTTCTTCACTTCAAA SEQ ID NO:527	-11.1	-17	54.4	-4.8	-1	-3.7
488	CAAATCTGTTGGAAGACTTG SEQ ID NO:528	-11	-18.8	57.6	-6.9	-0.7	-3.6
694	CTTATGCTATATCTAGAAAG SEQ ID NO:529	-11	-17	54.6	-6	0	-6.2
1498	GGTTTTTATTCTAACCATTT SEQ ID NO:530	-11	-20	61.5	-7.5	-1.4	-5.2
1545	AATAAATTTATCATGCCTCA SEQ ID NO:531	-11	-18.4	56.4	-6.9	0	-8.1
1693	TCTTCTTTTACAAACCTCCT SEQ ID NO:532	-11	-22.6	66.2	-11.6	0	-1.9
1694	TTCTTCTTTTACAAACCTCC SEQ ID NO:533	-11	-21.8	64.7	-10.8	0	-1.9
1848	ATTCTTAAATAAGTTCTTCA SEQ ID NO:534	-11	-16.6	54.2	-5.6	0	-4.9
232	CCGCCCTGCAGCGCACACTC SEQ ID NO:535	-10.9	-33.5	84.5	-20.9	-1.7	-10.5
399	CAGTTGCAGGTCTCTCTGCA SEQ ID NO:536	-10.9	-27.3	81.3	-12.9	-3.5	-9.9
552	TTCACAACTTCTTCTCTCAC SEQ ID NO:537	-10.9	-21.9	67.2	-11	0	-0.6
734	CACCATGCATCACAATTTGG SEQ ID NO:538	-10.9	-22.8	65.1	-11	-0.7	-6.6
736	TCCACCATGCATCACAATTT SEQ ID NO:539	-10.9	-24	67.7	-13.1	0	-6.6
791	TGTTCAGTCATATGGATGTT SEQ ID NO:540	-10.9	-21.5	66.6	-9.9	-0.4	-6.7
797	TACAAGTGTTCAGTCATATG SEQ ID NO:541	-10.9	-19.5	61.4	-8.6	0	-5.6
798	ATACAAGTGTTCAGTCATAT SEQ ID NO:542	-10.9	-19.5	61.5	-8.6	0	-3.7
1000	AGTCTTCATTCCATATCCCA SEQ ID NO:543	-10.9	-25.7	74.2	-14.8	0	-2
1123	GACTTTTCCCAAAGCCAAAA SEQ ID NO:544	-10.9	-22.1	61.7	-9.8	-1.3	-4.1
1185	TCAAATTTCCATAAGCTTCA SEQ ID NO:545	-10.9	-19.9	60	-9	0	-6.8
1201	CAAAGCTGTTTGTTACTCAA SEQ ID NO:546	-10.9	-19.9	60.6	-8.1	-0.8	-5.5
1646	AAAATTCACCGAAGTCACAG SEQ ID NO:547	-10.9	-19.2	57	-8.3	0	-3.5
70	CAGCAGCAAGACGCTCTTCA SEQ ID NO:548	-10.8	-25.8	72.9	-13.7	-1.2	-6
108	CAGGCGGCCACCAGGTGTGC SEQ ID NO:549	-10.8	-32.5	86.1	-19.9	-1.4	-11.3
380	AATCCATCCCGAAGGTGCCG SEQ ID NO:550	-10.8	-28.5	73.2	-16.4	-1.2	-6.2
581	TCATTACGGGAGACCCGGCA SEQ ID NO:551	-10.8	-28.2	74.4	-13.7	-3.7	-11
746	GTTTTCTGGATCCACCATGC SEQ ID NO:552	-10.8	-26.4	75.4	-14.2	-1.2	-9.7
905	TTGACCTGTCTCCATGTAAG SEQ ID NO:553	-10.8	-23.6	69.1	-12.8	0	-5.1
1131	TTTATTTTGACTTTTCCCAA SEQ ID NO:554	-10.8	-20.6	61.7	-9.8	0	-2.7
1148	AGGGGTTTTCTGGTTGTTTT SEQ ID NO:555	-10.8	-24.4	74.5	-13.6	0	-2
1203	TTCAAAGCTGTTTGTTACTC SEQ ID NO:556	-10.8	-20.4	63.3	-8.1	-1.4	-6

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1270	CCAGAACCGTCCTTCAGATA SEQ ID NO:557	-10.8	-25.6	70.7	-14.3	-0.2	-3.4
1643	ATTCACCGAAGTCACAGCAC SEQ ID NO:558	-10.8	-24	68.4	-13.2	0	-4.1
1645	AAATTCACCGAAGTCACAGC SEQ ID NO:559	-10.8	-21.7	62.6	-10.9	0	-3.5
1656	CCTTAAATTGAAAATTCACC SEQ ID NO:560	-10.8	-17.3	53	-5.6	-0.7	-5.7
1716	CATGTTTTCTGCTGAAAATT SEQ ID NO:561	-10.8	-18.8	57.8	-5.5	-2.5	-11.4
1915	CCTTCCACACACATTCACAA SEQ ID NO:562	-10.8	-24.2	67.9	-13.4	0	-0.9
71	TCAGCAGCAAGACGCTCTTC SEQ ID NO:563	-10.7	-25.5	73.5	-13.7	-1	-6
148	GTCACAGTGTTGAGGGCAGT SEQ ID NO:564	-10.7	-26.4	79.2	-15.7	0	-6
334	CTCTTCACCAAAAGGATCCT SEQ ID NO:565	-10.7	-23.3	66.3	-11.7	0	-9.7
526	GCCATCTCCAGATGCCATGT SEQ ID NO:566	-10.7	-29.2	80.3	-17.4	-1	-7.8
739	GGATCCACCATGCATCACAA SEQ ID NO:567	-10.7	-25.6	70.7	-14.2	-0.4	-8.3
1205	AGTTCAAAGCTGTTTGTTAC SEQ ID NO:568	-10.7	-20.3	63.2	-8.1	-1.4	-6
1513	CCTTATAGAGTCATAGGTTT SEQ ID NO:569	-10.7	-21.6	66.5	-10.9	0	-4.8
1836	GTTCTTCACTTCAAATAAAA SEQ ID NO:570	-10.7	-16.3	52.5	-5.6	0	-1.6
139	TTGAGGGCAGTCCACCGCAT SEQ ID NO:571	-10.6	-29.4	79.4	-17.7	-1	-5.6
353	AGTCTTTGCAGATACCAAAC SEQ ID NO:572	-10.6	-21.2	63.2	-10	-0.3	-5.2
989	CATATCCCAACATTAATGTA SEQ ID NO:573	-10.6	-19.7	58.6	-7.8	-0.2	-10.5
1001	AAGTCTTCATTCCATATCCC SEQ ID NO:574	-10.6	-24.3	70.6	-13.7	0	-2.4
1015	CTTCTCCTGCTCTTAAGTCT SEQ ID NO:575	-10.6	-25.2	75.4	-14.6	0	-6
1046	ATTTTATTTCCCACTCCCAC SEQ ID NO:576	-10.6	-25.7	72.1	-15.1	0	-0.5
1128	ATTTTGACTTTTCCCAAAGC SEQ ID NO:577	-10.6	-21.8	63.8	-9.8	-1.3	-6.3
1914	CTTCCACACACATTCACAAC SEQ ID NO:578	-10.6	-22.4	64.9	-11.8	0	-1
186	GTCCTCTTGCAGCGCGGGCT SEQ ID NO:579	-10.5	-32.7	87.5	-20.7	-1.3	-10
265	CATGCCTGAGACTGTGCGGT SEQ ID NO:580	-10.5	-27.9	76.9	-16.8	-0.3	-5.3
745	TTTTCTGGATCCACCATGCA SEQ ID NO:581	-10.5	-25.9	73.1	-14.2	-1	-9.5
863	TTCTTCAGTGTTACTATACA SEQ ID NO:582	-10.5	-20.2	63.8	-9.7	0	-3.5
986	ATCCCAACATTAATGTACAT SEQ ID NO:583	-10.5	-20.2	59.7	-8.4	-0.2	-10.5
1217	GAAATTGCTCTCAGTTCAAA SEQ ID NO:584	-10.5	-19.4	59.4	-8.9	0	-4.2
1337	TCTTAGATTTATCTCTGAGG SEQ ID NO:585	-10.5	-20	63.3	-8.6	-0.7	-6.2
1432	GGGTAGGGAAGATGACTTGC SEQ ID NO:586	-10.5	-23.8	69.8	-12.4	-0.7	-4

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1717	ACATGTTTTCTGCTGAAAAT SEQ ID NO:587	-10.5	-18.9	58	-6.4	-2	-10.9
1974	TAATAAACATGTCCTTTTAA SEQ ID NO:588	-10.5	-16	51.5	-5.5	0	-6.9
44	CCAGCTGCCTCCGGCTCGGC SEQ ID NO:589	-10.4	-35.4	89.9	-22.9	-2.1	-10.8
66	AGCAAGACGCTCTTCATGTT SEQ ID NO:590	-10.4	-23.9	69.6	-12.3	-1.1	-6.8
107	AGGCGGCCACCAGGTGTGCA SEQ ID NO:591	-10.4	-32.5	86.1	-19.9	-2	-11.8
128	CCACCGCATAATTATTGCTC SEQ ID NO:592	-10.4	-24.2	67.3	-12.9	-0.7	-7.9
335	ACTCTTCACCAAAAGGATCC SEQ ID NO:593	-10.4	-22.6	65	-11.7	0	-7.7
1043	TTATTTCCCACTCCCACCCC SEQ ID NO:594	-10.4	-31.5	81.4	-21.1	0	-0.7
1290	GTGTATGTGTTTCCTATGCC SEQ ID NO:595	-10.4	-25.5	75.4	-15.1	0	-3
1516	AAACCTTATAGAGTCATAGG SEQ ID NO:596	-10.4	-19	58.7	-8.6	0	-5
1652	AAATTGAAAATTCACCGAAG SEQ ID NO:597	-10.4	-15.3	48.8	-3.6	-1.2	-5.7
1695	ATTCTTCTTTTACAAACCTC SEQ ID NO:598	-10.4	-19.8	60.9	-9.4	0	-1.9
1981	TGAACAATAATAAACATGTC SEQ ID NO:599	-10.4	-13.9	47	-3.5	0	-6.9
122	CATAATTATTGCTCCAGGCG SEQ ID NO:600	-10.3	-23.2	65.9	-11.4	-1.4	-9.3
867	TTAGTTCTTCAGTGTTACTA SEQ ID NO:601	-10.3	-20.6	66.1	-10.3	0	-4.1
944	CTCACTGCGGTCTTCAGCTT SEQ ID NO:602	-10.3	-27.4	78.9	-16.4	-0.5	-6.2
1511	TTATAGAGTCATAGGTTTTT SEQ ID NO:603	-10.3	-18.9	61	-8.6	0	-4
1588	TTGACATTTTTTGAAATCCA SEQ ID NO:604	-10.3	-18.4	56.6	-7.2	-0.7	-5
1655	CTTAAATTGAAAATTCACCG SEQ ID NO:605	-10.3	-16.1	50.4	-4.5	-1.2	-5.7
138	TGAGGGCAGTCCACCGCATA SEQ ID NO:606	-10.2	-29	78.5	-17.7	-1	-5.6
368	AGGTGCCGTAGGGACAGTCT SEQ ID NO:607	-10.2	-28.3	80.5	-17	-1	-7.9
590	ACCATTTCCTCATTACGGGA SEQ ID NO:608	-10.2	-25.3	70.6	-14.6	-0.1	-4
628	TTCTCTCAGAAATCACAGCC SEQ ID NO:609	-10.2	-22.8	67.4	-11.9	-0.4	-4
634	AGAGCCTTCTCTCAGAAATC SEQ ID NO:610	-10.2	-22.7	68.1	-10.9	-1.5	-5.1
635	TAGAGCCTTCTCTCAGAAAT SEQ ID NO:611	-10.2	-22	65.9	-10.1	-1.7	-6.4
744	TTTCTGGATCCACCATGCAT SEQ ID NO:612	-10.2	-25.8	72.7	-14.2	-1.2	-9.7
1195	TGTTTGTTACTCAAATTTCC SEQ ID NO:613	-10.2	-19.8	61	-8	-1.6	-4.6
1238	GAACTACATCAGCAGCCTTT SEQ ID NO:614	-10.2	-24.1	69.6	-13.9	0	-4.5
1253	ATACAGGTAACCCGGGAACT SEQ ID NO:615	-10.2	-24.4	67.1	-12.7	-0.2	-11
1361	CAAACCACCAGTGGGTAAAA SEQ ID NO:616	-10.2	-21.5	60.7	-10	-1.2	-9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1492	TATTCTAACCATTTTCAACA SEQ ID NO:617	-10.2	-18.6	57.3	-8.4	0	-1.2
213	CGGCAGCAGCCACAGTCGTC SEQ ID NO:618	-10.1	-30.4	82.5	-17.1	-3.2	-9.8
363	CCGTAGGGACAGTCTTTGCA SEQ ID NO:619	-10.1	-26.8	75.8	-15.8	-0.8	-7.9
434	ATTTTCCCGTCCCCCTGTCA SEQ ID NO:620	-10.1	-32.3	84.3	-22.2	0	-2.6
576	ACGGGAGACCCGGCAGCATT SEQ ID NO:621	-10.1	-29.9	77.6	-16.1	-3.7	-12.1
737	ATCCACCATGCATCACAATT SEQ ID NO:622	-10.1	-23.9	67.3	-13.8	0	-6.6
1016	TCTTCTCCTGCTCTTAAGTC SEQ ID NO:623	-10.1	-24.7	75.1	-14.6	0	-6
1134	TGTTTTATTTTGACTTTTCC SEQ ID NO:624	-10.1	-19.9	62.2	-9.8	0	-2.5
1154	TCCTTCAGGGGTTTTCTGGT SEQ ID NO:625	-10.1	-27.3	80.7	-16.7	-0.2	-5.7
1244	ACCCGGGAACTACATCAGCA SEQ ID NO:626	-10.1	-26.6	71.7	-15.2	0.3	-10.7
1653	TAAATTGAAAATTCACCGAA SEQ ID NO:627	-10.1	-15	48.2	-3.6	-1.2	-5.4
1901	TCACAACTCTGTTGGCCAAC SEQ ID NO:628	-10.1	-24.2	69.2	-11.1	-1.8	-14
1982	TTGAACAATAATAAACATGT SEQ ID NO:629	-10.1	-13.6	46.3	-3.5	0	-6.7
129	TCCACCGCATAATTATTGCT SEQ ID NO:630	-10	-24.2	67.3	-12.9	-1.2	-8.4
157	CTCACTGCTGTCACAGTGTT SEQ ID NO:631	-10	-25.5	76.3	-12.1	-3.4	-9.7
396	TTGCAGGTCTCTCTGCAATC SEQ ID NO:632	-10	-25.1	75	-10.7	-4.4	-11.4
643	CACGAAAATAGAGCCTTCTC SEQ ID NO:633	-10	-21	61.2	-10.1	-0.7	-4.9
1005	TCTTAAGTCTTCATTCCATA SEQ ID NO:634	-10	-21	64.8	-11	0	-6
1040	TTTCCCACTCCCACCCCCTC SEQ ID NO:635	-10	-35	88.2	-25	0	0
1546	TAATAAATTTATCATGCCTC SEQ ID NO:636	-10	-17.4	54.6	-6.9	0	-8.1
1999	TATCTTGTTCTTTTTTATTG SEQ ID NO:637	-10	-18	58.7	-8	0	-0.9
109	CCAGGCGGCCACCAGGTGTG SEQ ID NO:638	-9.9	-32.7	85.1	-21.6	-0.6	-10.2
119	AATTATTGCTCCAGGCGGCC SEQ ID NO:639	-9.9	-27.8	75.3	-16.4	-1.4	-8.9
162	TTGCACTCACTGCTGTCACA SEQ ID NO:640	-9.9	-25.8	75	-14	-1.9	-5.9
755	CTACTTTTTGTTTTCTGGAT SEQ ID NO:641	-9.9	-20.7	64.3	-10.8	0	-2.6
1245	AACCCGGGAACTACATCAGC SEQ ID NO:642	-9.9	-25.2	68.6	-13.9	-0.2	-10.7
1254	GATACAGGTAACCCGGGAAC SEQ ID NO:643	-9.9	-24.1	66.5	-12.7	-0.9	-10.7
1412	ACTAACACATTTATTTATAA SEQ ID NO:644	-9.9	-14.7	49.3	-4.8	0	-3.7
1415	TGCACTAACACATTTATTTA SEQ ID NO:645	-9.9	-18.2	56.7	-8.3	0	-4.7
1794	AACATCTAGTACAACAGTCC SEQ ID NO:646	-9.9	-20.8	62.9	-10.9	0	-5.3

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1896	ACTCTGTTGGCCAACTTCAA SEQ ID NO:647	-9.9	-24.3	69.8	-11.3	0.2	-14.3
38	GCCTCCGGCTCGGCTCTCCA SEQ ID NO:648	-9.8	-35.3	91.1	-23.4	-2.1	-9.2
161	TGCACTCACTGCTGTCACAG SEQ ID NO:649	-9.8	-25.7	74.9	-14	-1.9	-6.2
553	TTTCACAACTTCTTCTCTCA SEQ ID NO:650	-9.8	-21.8	67	-12	0	-0.7
627	TCTCTCAGAAATCACAGCCG SEQ ID NO:651	-9.8	-23.5	67.3	-13.7	0	-3.2
640	GAAAATAGAGCCTTCTCTCA SEQ ID NO:652	-9.8	-21.3	63.5	-9.8	-1.7	-5.1
644	TCACGAAAATAGAGCCTTCT SEQ ID NO:653	-9.8	-21	61.2	-11.2	0	-3.5
695	ACTTATGCTATATCTAGAAA SEQ ID NO:654	-9.8	-17.2	55	-7.4	0	-6.2
1047	TATTTTATTTCCCACTCCCA SEQ ID NO:655	-9.8	-25.2	71	-15.4	0	-0.7
1491	ATTCTAACCATTTTCAACAA SEQ ID NO:656	-9.8	-18.2	56	-8.4	0	-1.2
1502	CATAGGTTTTTATTCTAACC SEQ ID NO:657	-9.8	-19.5	60.4	-8.5	-1.1	-4.6
1840	ATAAGTTCTTCACTTCAAAT SEQ ID NO:658	-9.8	-17.7	56.3	-6.8	-1	-3.6
1916	GCCTTCCACACACATTCACA SEQ ID NO:659	-9.8	-26.7	74.2	-16.9	0	-2
333	TCTTCACCAAAAGGATCCTC SEQ ID NO:660	-9.7	-22.8	65.9	-12.1	0	-9.9
400	GCAGTTGCAGGTCTCTCTGC SEQ ID NO:661	-9.7	-28.4	85.2	-16.3	-2.4	-8.2
490	AACAAATCTGTTGGAAGACT SEQ ID NO:662	-9.7	-18.2	56	-6.9	-1.6	-5
641	CGAAAATAGAGCCTTCTCTC SEQ ID NO:663	-9.7	-21.4	62.7	-10	-1.7	-5.4
1255	AGATACAGGTAACCCGGGAA SEQ ID NO:664	-9.7	-23.9	66.2	-12.7	-0.9	-10.7
1424	AAGATGACTTGCACTAACAC SEQ ID NO:665	-9.7	-19.4	58.8	-9.2	-0.1	-5
1654	TTAAATTGAAAATTCACCGA SEQ ID NO:666	-9.7	-15.8	49.9	-4.8	-1.2	-5.7
1701	AAATTGATTCTTCTTTTACA SEQ ID NO:667	-9.7	-17	54.8	-7.3	0	-3.2
164	TTTTGCACTCACTGCTGTCA SEQ ID NO:668	-9.6	-25.1	74	-13.6	-1.9	-5
389	TCTCTCTGCAATCCATCCCG SEQ ID NO:669	-9.6	-28	76.3	-18.4	0	-4.9
466	TACTGAATATTGGAAGAAGG SEQ ID NO:670	-9.6	-16.7	53	-7.1	0	-4
1004	CTTAAGTCTTCATTCCATAT SEQ ID NO:671	-9.6	-20.6	63.2	-11	0	-4.8
1048	ATATTTTATTTCCCACTCCC SEQ ID NO:672	-9.6	-24.5	69.8	-14.9	0	-1.8
1122	ACTTTTCCCAAAGCCAAAAA SEQ ID NO:673	-9.6	-20.8	58.9	-9.8	-1.3	-4.2
1222	CTTTTGAAATTGCTCTCAGT SEQ ID NO:674	-9.6	-20.8	63.4	-11.2	0	-3.6
1340	ACTTCTTAGATTTATCTCTG SEQ ID NO:675	-9.6	-19.4	61.9	-8.9	-0.7	-5.1
1547	ATAATAAATTTATCATGCCT SEQ ID NO:676	-9.6	-17	53.4	-6.9	0	-8.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1998	ATCTTGTTCTTTTTTATTGA SEQ ID NO:677	-9.6	-18.9	60.7	-9.3	0	-2.3
137	GAGGGCAGTCCACCGCATAA SEQ ID NO:678	-9.5	-28.3	76.3	-17.7	-1	-5.6
149	TGTCACAGTGTTGAGGGCAG SEQ ID NO:679	-9.5	-25.2	75.2	-15.7	0	-6
310	ATTAGAAGGCTGACACCTCA SEQ ID NO:680	-9.5	-23.3	67.7	-13	-0.6	-4.3
316	CTCCCCATTAGAAGGCTGAC SEQ ID NO:681	-9.5	-26.4	73.1	-16.9	0	-3.7
474	GACTTGGTTACTGAATATTG SEQ ID NO:682	-9.5	-18.8	58.5	-9.3	0	-4.6
729	TGCATCACAATTTGGATCTT SEQ ID NO:683	-9.5	-21.2	63.5	-11.7	0	-5.4
740	TGGATCCACCATGCATCACA SEQ ID NO:684	-9.5	-26.3	72.8	-15.5	-1.1	-9.6
1236	ACTACATCAGCAGCCTTTTG SEQ ID NO:685	-9.5	-24.3	70.9	-14.8	0	-4.5
1494	TTTATTCTAACCATTTTCAA SEQ ID NO:686	-9.5	-17.9	56.2	-8.4	0	-1.4
1520	TTGAAAACCTTATAGAGTCA SEQ ID NO:687	-9.5	-18.1	56.2	-8.6	0	-4.8
1585	ACATTTTTTGAAATCCAGAG SEQ ID NO:688	-9.5	-18.3	56.6	-7.8	-0.9	-4.3
1788	TAGTACAACAGTCCTGTTTG SEQ ID NO:689	-9.5	-21.6	65.6	-11.1	-0.9	-8.4
151	GCTGTCACAGTGTTGAGGGC SEQ ID NO:690	-9.4	-27.2	80.6	-17.1	-0.4	-7.4
636	ATAGAGCCTTCTCTCAGAAA SEQ ID NO:691	-9.4	-22	65.9	-10.9	-1.7	-6.4
674	TTCCTAAAATGTTGGCTGTG SEQ ID NO:692	-9.4	-21.4	63.2	-12	0	-3.9
730	ATGCATCACAATTTGGATCT SEQ ID NO:693	-9.4	-21.1	63.1	-11.7	0	-6.4
1130	TTATTTTGACTTTTCCCAAA SEQ ID NO:694	-9.4	-19.8	59.5	-9.8	-0.3	-3.7
1153	CCTTCAGGGGTTTTCTGGTT SEQ ID NO:695	-9.4	-27	79.2	-16.7	-0.7	-4.2
1191	TGTTACTCAAATTTCCATAA SEQ ID NO:696	-9.4	-18.1	56.2	-8.7	0	-4.5
1519	TGAAAACCTTATAGAGTCAT SEQ ID NO:697	-9.4	-18	55.9	-8.6	0	-4.8
1603	TCTGTTGCTCATTTTTTGAC SEQ ID NO:698	-9.4	-21.7	66.9	-11.8	-0.1	-3.3
1775	CTGTTTGTGCTAAGATTCTT SEQ ID NO:699	-9.4	-21.3	65.5	-11.9	0	-5.4
1895	CTCTGTTGGCCAACTTCAAG SEQ ID NO:700	-9.4	-24.1	69.5	-11.3	-0.5	-15
41	GCTGCCTCCGGCTCGGCTCT SEQ ID NO:701	-9.3	-34.9	91.1	-23.5	-2.1	-10
121	ATAATTATTGCTCCAGGCGG SEQ ID NO:702	-9.3	-23.7	67.2	-12.9	-1.4	-9.3
163	TTTGCACTCACTGCTGTCAC SEQ ID NO:703	-9.3	-25.2	74.3	-14	-1.9	-5
572	GAGACCCGGCAGCATTCTCT SEQ ID NO:704	-9.3	-29.1	79.5	-19.1	-0.5	-5.8
580	CATTACGGGAGACCCGGCAG SEQ ID NO:705	-9.3	-27.8	73.2	-15.7	-2.8	-10.1
956	GAACTAATTTGACTCACTGC SEQ ID NO:706	-9.3	-19.9	60.4	-10.6	0	-2.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
999	GTCTTCATTCCATATCCCAA SEQ ID NO:707	-9.3	-25	71.5	-15.7	0	-2
1045	TTTTATTTCCCACTCCCACC SEQ ID NO:708	-9.3	-27.7	75.6	-18.4	0	-0.7
1638	CCGAAGTCACAGCACTTATG SEQ ID NO:709	-9.3	-23.3	66.5	-13.3	-0.5	-4.6
117	TTATTGCTCCAGGCGGCCAC SEQ ID NO:710	-9.2	-29.4	79.4	-19	-0.7	-10.2
215	CTCGGCAGCAGCCACAGTCG SEQ ID NO:711	-9.2	-30.1	80.9	-17.7	-3.2	-9.8
303	GGCTGACACCTCAGCCCCGG SEQ ID NO:712	-9.2	-33.4	85.2	-18.8	-5.3	-18.2
630	CCTTCTCTCAGAAATCACAG SEQ ID NO:713	-9.2	-21.9	65.2	-11.9	-0.6	-4.3
731	CATGCATCACAATTTGGATC SEQ ID NO:714	-9.2	-20.9	62.4	-11.7	0	-6.6
754	TACTTTTTGTTTTCTGGATC SEQ ID NO:715	-9.2	-20.2	63.8	-11	0	-4.1
756	CCTACTTTTTGTTTTCTGGA SEQ ID NO:716	-9.2	-22.7	68.2	-13.5	0	-2.7
1066	CTACCAAGGAAGGGCTAAAT SEQ ID NO:717	-9.2	-21.3	61.3	-12.1	0	-3.8
1149	CAGGGGTTTTCTGGTTGTTT SEQ ID NO:718	-9.2	-25	75.3	-15.3	-0.1	-3.6
1365	CACACAAACCACCAGTGGGT SEQ ID NO:719	-9.2	-25.7	70.3	-15.2	-1.2	-9
1909	ACACACATTCACAACTCTGT SEQ ID NO:720	-9.2	-21.7	64.6	-12.5	0	-2.5
39	TGCCTCCGGCTCGGCTCTCC SEQ ID NO:721	-9.1	-34.6	90	-23.4	-2.1	-10
582	CTCATTACGGGAGACCCGGC SEQ ID NO:722	-9.1	-28.4	75.2	-15.6	-3.7	-11
584	TCCTCATTACGGGAGACCCG SEQ ID NO:723	-9.1	-27.8	73.7	-15.4	-3.3	-10.5
673	TCCTAAAATGTTGGCTGTGT SEQ ID NO:724	-9.1	-22.5	65.9	-13.4	0	-3.9
987	TATCCCAACATTAATGTACA SEQ ID NO:725	-9.1	-19.9	59.1	-9.5	-0.2	-10.5
1184	CAAATTTCCATAAGCTTCAA SEQ ID NO:726	-9.1	-18.8	56.8	-9.7	0	-6.8
1212	TGCTCTCAGTTCAAAGCTGT SEQ ID NO:727	-9.1	-24	71.8	-13.5	-1.3	-6.2
1490	TTCTAACCATTTTCAACAAA SEQ ID NO:728	-9.1	-17.5	54.2	-8.4	0	-1.9
1518	GAAAACCTTATAGAGTCATA SEQ ID NO:729	-9.1	-17.7	55.4	-8.6	0	-4.8
1584	CATTTTTTGAAATCCAGAGT SEQ ID NO:730	-9.1	-19.3	59	-9.2	-0.9	-4.3
1842	AAATAAGTTCTTCACTTCAA SEQ ID NO:731	-9.1	-17	54.4	-6.8	-1	-4.2
1894	TCTGTTGGCCAACTTCAAGA SEQ ID NO:732	-9.1	-23.8	68.9	-11.3	-0.5	-15
43	CAGCTGCCTCCGGCTCGGCT SEQ ID NO:733	-9	-34.3	88.6	-22.9	-2.4	-9.9
135	GGGCAGTCCACCGCATAATT SEQ ID NO:734	-9	-27.8	75	-17.7	-1	-4.9
140	GTTGAGGGCAGTCCACCGCA SEQ ID NO:735	-9	-30.6	83	-20.5	-1	-4.8
150	CTGTCACAGTGTTGAGGGCA SEQ ID NO:736	-9	-26.1	76.9	-17.1	0	-6

position	oligo	kcal/ mol total binding	kcal/ mol duplex form-ation	deg C Tm of Duplex	kcal/ mol target struc-ture	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
629	CTTCTCTCAGAAATCACAGC SEQ ID NO:737	-9	-21.7	65.6	-11.9	-0.6	-3.9
747	TGTTTTCTGGATCCACCATG SEQ ID NO:738	-9	-24.6	70.9	-14.2	-1.2	-9.7
757	TCCTACTTTTTGTTTTCTGG SEQ ID NO:739	-9	-22.5	68.5	-13.5	0	-2.9
949	TTTGACTCACTGCGGTCTTC SEQ ID NO:740	-9	-24.9	73.1	-14.9	-0.9	-6.2
1225	AGCCTTTTGAAATTGCTCTC SEQ ID NO:741	-9	-22.7	67	-13.7	0	-5.4
1252	TACAGGTAACCCGGGAACTA SEQ ID NO:742	-9	-24.1	66.6	-13.7	-1.1	-10.2
1366	ACACACAAACCACCAGTGGG SEQ ID NO:743	-9	-24.7	67.8	-14.4	-1.2	-9
1489	TCTAACCATTTTCAACAAAT SEQ ID NO:744	-9	-17.4	53.9	-8.4	0	-2.5
1507	AGAGTCATAGGTTTTTATTC SEQ ID NO:745	-9	-19.6	63.2	-10.6	0	-4.8
1623	TTATGTTTAAATAAGGTCCC SEQ ID NO:746	-9	-19.3	58.8	-10.3	0	-4.3
136	AGGGCAGTCCACCGCATAAT SEQ ID NO:747	-8.9	-27.7	75	-17.7	-1	-5.6
347	TGCAGATACCAAACTCTTCA SEQ ID NO:748	-8.9	-21.9	64.1	-13	0	-4.7
983	CCAACATTAATGTACATCAA SEQ ID NO:749	-8.9	-18.2	55.4	-8	-0.2	-10.5
1017	ATCTTCTCCTGCTCTTAAGT SEQ ID NO:750	-8.9	-24.3	73.2	-15.4	0	-6
1213	TTGCTCTCAGTTCAAAGCTG SEQ ID NO:751	-8.9	-22.9	68.7	-12.8	-1.1	-5.6
1525	GATGTTTGAAAACCTTATAG SEQ ID NO:752	-8.9	-17.1	53.9	-7.7	-0.1	-5.7
1702	AAAATTGATTCTTCTTTTAC SEQ ID NO:753	-8.9	-15.6	51.6	-6.7	0	-3.2
1973	AATAAACATGTCCTTTTAAA SEQ ID NO:754	-8.9	-15.6	50.4	-6.7	0	-6.4
1983	ATTGAACAATAATAAACATG SEQ ID NO:755	-8.9	-12.4	43.9	-3.5	0	-5.3
106	GGCGGCCACCAGGTGTGCAG SEQ ID NO:756	-8.8	-32.5	86.1	-21.1	-2.5	-12.5
270	CCATCCATGCCTGAGACTGT SEQ ID NO:757	-8.8	-28	76.9	-19.2	0	-3.8
544	TTCTTCTCTCACAATATTGC SEQ ID NO:758	-8.8	-21	64.8	-11.6	0	-8.5
749	TTTGTTTTCTGGATCCACCA SEQ ID NO:759	-8.8	-24.8	71.8	-14.7	-1.1	-9.7
1013	TCTCCTGCTCTTAAGTCTTC SEQ ID NO:760	-8.8	-24.7	75.1	-15.9	0	-6
1018	CATCTTCTCCTGCTCTTAAG SEQ ID NO:761	-8.8	-23.8	70.9	-15	0	-5.4
1143	TTTTCTGGTTGTTTTATTTT SEQ ID NO:762	-8.8	-19.6	62.6	-10.8	0	-1.5
1211	GCTCTCAGTTCAAAGCTGTT SEQ ID NO:763	-8.8	-24.1	72.4	-14.4	-0.7	-5.4
1226	CAGCCTTTTGAAATTGCTCT SEQ ID NO:764	-8.8	-23	66.7	-13.7	-0.1	-5.5
1243	CCCGGGAACTACATCAGCAG SEQ ID NO:765	-8.8	-26.4	71.5	-16.8	-0.2	-9.2
1283	TGTTTCCTATGCCCCAGAAC SEQ ID NO:766	-8.8	-27	74.1	-18.2	0	-3

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1755	TCAAATATACTCCTAATTCC SEQ ID NO:767	-8.8	-19	57.8	-10.2	0	-2.9
72	GTCAGCAGCAAGACGCTCTT SEQ ID NO:768	-8.7	-26.3	75.2	-16.3	-1.2	-7.9
666	ATGTTGGCTGTGTGTTGAAC SEQ ID NO:769	-8.7	-23	69.1	-14.3	0	-4
696	TACTTATGCTATATCTAGAA SEQ ID NO:770	-8.7	-17.6	56.3	-8.9	0	-6.2
886	GATTACCTAAATTGCATTTT SEQ ID NO:771	-8.7	-18.7	57.2	-10	0	-6
1129	TATTTTGACTTTTCCCAAAG SEQ ID NO:772	-8.7	-19.7	59.3	-9.8	-1.1	-5
1258	TTCAGATACAGGTAACCCGG SEQ ID NO:773	-8.7	-24	67.5	-14.3	-0.9	-5.8
1777	TCCTGTTTGTGCTAAGATTC SEQ ID NO:774	-8.7	-22.7	68.6	-14	0	-3.6
1965	TGTCCTTTTAAAACAAAACC SEQ ID NO:775	-8.7	-17.4	53.3	-8.2	-0.1	-6
158	ACTCACTGCTGTCACAGTGT SEQ ID NO:776	-8.6	-25.6	76.5	-13.6	-3.4	-9.7
750	TTTTGTTTTCTGGATCCACC SEQ ID NO:777	-8.6	-24.2	71	-14.7	0	-9.7
878	AAATTGCATTTTTAGTTCTT SEQ ID NO:778	-8.6	-18	57.2	-9.4	0	-5.8
887	AGATTACCTAAATTGCATTT SEQ ID NO:779	-8.6	-18.6	57.1	-10	0	-5.3
900	CTGTCTCCATGTAAGATTAC SEQ ID NO:780	-8.6	-21.3	64.8	-12.7	0	-5.5
950	ATTTGACTCACTGCGGTCTT SEQ ID NO:781	-8.6	-24.5	71.4	-14.9	-0.9	-6.2
1144	GTTTTCTGGTTGTTTTATTT SEQ ID NO:782	-8.6	-20.7	65.7	-12.1	0	-1.5
1289	TGTATGTGTTTCCTATGCCC SEQ ID NO:783	-8.6	-26.3	75.5	-17.7	0	-3
1414	GCACTAACACATTTATTTAT SEQ ID NO:784	-8.6	-18.2	56.8	-9.6	0	-3.4
1774	TGTTTGTGCTAAGATTCTTT SEQ ID NO:785	-8.6	-20.5	63.8	-11.9	0	-5.6
1984	TATTGAACAATAATAAACAT SEQ ID NO:786	-8.6	-12.1	43.4	-3.5	0	-6.5
268	ATCCATGCCTGAGACTGTGC SEQ ID NO:787	-8.5	-27.1	76.4	-18.6	0	-4.2
492	GAAACAAATCTGTTGGAAGA SEQ ID NO:788	-8.5	-17	53.2	-6.9	-1.5	-5
494	GAGAAACAAATCTGTTGGAA SEQ ID NO:789	-8.5	-17	53.2	-6.9	-1.5	-5
571	AGACCCGGCAGCATTCTCTT SEQ ID NO:790	-8.5	-28.6	78.6	-20.1	0	-6.3
595	ATTTAACCATTTCCTCATTA SEQ ID NO:791	-8.5	-20.5	61.5	-12	0	-2.4
882	ACCTAAATTGCATTTTTAGT SEQ ID NO:792	-8.5	-19.3	59	-9.6	-0.9	-9.6
1155	TTCCTTCAGGGGTTTTCTGG SEQ ID NO:793	-8.5	-26.2	77.3	-16.8	-0.7	-5.7
1196	CTGTTTGTTACTCAAATTTC SEQ ID NO:794	-8.5	-18.7	59.1	-8.6	-1.6	-4.6
1339	CTTCTTAGATTTATCTCTGA SEQ ID NO:795	-8.5	-19.8	62.8	-10.4	-0.7	-5.1
1517	AAAACCTTATAGAGTCATAG SEQ ID NO:796	-8.5	-17.1	54.3	-8.6	0	-4.8

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
1615	AAATAAGGTCCCTCTGTTGC SEQ ID NO:797	-8.5	-23.7	68.4	-15.2	0	-4.2
1843	TAAATAAGTTCTTCACTTCA SEQ ID NO:798	-8.5	-17.4	55.8	-8	-0.7	-4.2
269	CATCCATGCCTGAGACTGTG SEQ ID NO:799	-8.4	-26	73.2	-17.6	0	-4.2
361	GTAGGGACAGTCTTTGCAGA SEQ ID NO:800	-8.4	-24.6	74	-16.2	0	-5.9
402	TGGCAGTTGCAGGTCTCTCT SEQ ID NO:801	-8.4	-27.8	83.1	-18.5	-0.7	-6.6
667	AATGTTGGCTGTGTGTTGAA SEQ ID NO:802	-8.4	-22.1	66.1	-13.7	0	-3.7
733	ACCATGCATCACAATTTGGA SEQ ID NO:803	-8.4	-22.7	65.2	-13.1	-1.1	-6.6
786	AGTCATATGGATGTTATGGA SEQ ID NO:804	-8.4	-20.6	63.5	-11.5	-0.4	-6.2
1064	ACCAAGGAAGGGCTAAATAT SEQ ID NO:805	-8.4	-20.4	59.5	-12	0	-3.8
1209	TCTCAGTTCAAAGCTGTTTG SEQ ID NO:806	-8.4	-21.5	66	-11.7	-1.3	-6.8
227	CTGCAGCGCACACTCGGCAG SEQ ID NO:807	-8.3	-29.4	78.6	-19.6	-1.4	-8.1
264	ATGCCTGAGACTGTGCGGTA SEQ ID NO:808	-8.3	-26.9	75.3	-18	-0.3	-5.4
348	TTGCAGATACCAAACTCTTC SEQ ID NO:809	-8.3	-21.3	63.3	-13	0	-5.2
575	CGGGAGACCCGGCAGCATTC SEQ ID NO:810	-8.3	-30.1	78.7	-19	-2.8	-11
884	TTACCTAAATTGCATTTTTA SEQ ID NO:811	-8.3	-17.9	55.7	-9.6	0	-6.2
951	AATTTGACTCACTGCGGTCT SEQ ID NO:812	-8.3	-23.7	68.7	-14.9	-0.2	-6.2
998	TCTTCATTCCATATCCCAAC SEQ ID NO:813	-8.3	-24	68.8	-15.7	0	-2
1063	CCAAGGAAGGGCTAAATATT SEQ ID NO:814	-8.3	-20.3	59.4	-12	0	-4.4
1206	CAGTTCAAAGCTGTTTGTTA SEQ ID NO:815	-8.3	-20.8	63.9	-11.6	-0.8	-6.2
1505	AGTCATAGGTTTTTATTCTA SEQ ID NO:816	-8.3	-19.6	63	-11.3	0	-2.4
1700	AATTGATTCTTCTTTTACAA SEQ ID NO:817	-8.3	-17	54.8	-8.7	0	-3.3
1839	TAAGTTCTTCACTTCAAATA SEQ ID NO:818	-8.3	-17.4	55.8	-8	-1	-3.6
272	TGCCATCCATGCCTGAGACT SEQ ID NO:819	-8.2	-28.6	77.7	-20.4	0	-4.2
295	CCTCAGCCCCGGGCCACACT SEQ ID NO:820	-8.2	-35.5	88.1	-25.9	-1	-10.4
433	TTTTCCCGTCCCCCTGTCAC SEQ ID NO:821	-8.2	-32.5	85	-24.3	0	-2.6
732	CCATGCATCACAATTTGGAT SEQ ID NO:822	-8.2	-22.5	64.6	-13.8	-0.2	-6.6
741	CTGGATCCACCATGCATCAC SEQ ID NO:823	-8.2	-26.5	73.6	-16.9	-1.2	-9.7
945	ACTCACTGCGGTCTTCAGCT SEQ ID NO:824	-8.2	-27.5	79.1	-18.6	-0.5	-6.2
1126	TTTGACTTTTCCCAAAGCCA SEQ ID NO:825	-8.2	-24.4	68.1	-15.5	-0.4	-6
1135	TTGTTTTATTTTGACTTTTC SEQ ID NO:826	-8.2	-18	58.5	-9.8	0	-2.5

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1972	ATAAACATGTCCTTTTAAAA SEQ ID NO:827	-8.2	-15.6	50.4	-7.4	0	-6.9
51	ATGTTTCCCAGCTGCCTCCG SEQ ID NO:828	-8.1	-31.1	82.6	-22.5	0	-8.1
271	GCCATCCATGCCTGAGACTG SEQ ID NO:829	-8.1	-28.6	77.7	-20.5	0	-4.2
491	AAACAAATCTGTTGGAAGAC SEQ ID NO:830	-8.1	-16.6	52.5	-6.9	-1.5	-5
574	GGGAGACCCGGCAGCATTCT SEQ ID NO:831	-8.1	-30.2	80.9	-20.7	-1.3	-8.1
895	TCCATGTAAGATTACCTAAA SEQ ID NO:832	-8.1	-19.1	57.6	-11	0	-4.3
1065	TACCAAGGAAGGGCTAAATA SEQ ID NO:833	-8.1	-20.1	59	-12	0	-3.8
1411	CTAACACATTTATTTATAAA SEQ ID NO:834	-8.1	-13.8	47.2	-4.8	-0.7	-6.1
1665	ATTTCATACCTTAAATTGA SEQ ID NO:835	-8.1	-17.3	54.6	-9.2	0	-3.2
1900	CACAACTCTGTTGGCCAACT SEQ ID NO:836	-8.1	-24.7	69.6	-13.2	-1.8	-15
1989	TTTTTATTGAACAATAATA SEQ ID NO:837	-8.1	-13.1	45.9	-4.1	-0.6	-9
1990	CTTTTTTATTGAACAATAAT SEQ ID NO:838	-8.1	-14.3	48.3	-5.5	-0.3	-8.7
1992	TTCTTTTTTATTGAACAATA SEQ ID NO:839	-8.1	-15.5	51.4	-7.4	0	-6.7
52	CATGTTTCCCAGCTGCCTCC SEQ ID NO:840	-8	-31	84.2	-22.5	0	-8.1
315	TCCCCATTAGAAGGCTGACA SEQ ID NO:841	-8	-26.2	72.3	-18.2	0	-3.7
362	CGTAGGGACAGTCTTTGCAG SEQ ID NO:842	-8	-24.8	72.4	-16.3	-0.1	-6
546	ACTTCTTCTCTCACAATATT SEQ ID NO:843	-8	-20.3	63.1	-12.3	0	-3.8
591	AACCATTTCCTCATTACGGG SEQ ID NO:844	-8	-24	67.2	-16	0	-3.6
596	GATTTAACCATTTCCTCATT SEQ ID NO:845	-8	-21.4	63.4	-13.4	0	-2.4
1548	GATAATAAATTTATCATGCC SEQ ID NO:846	-8	-16.7	52.8	-6.9	-1.8	-8.1
1718	GACATGTTTTCTGCTGAAAA SEQ ID NO:847	-8	-19.5	59.2	-9.2	-2.3	-11.2
1985	TTATTGAACAATAATAAACA SEQ ID NO:848	-8	-12.2	43.7	-3.5	-0.3	-8.5
14	TGGTCTTTGCTGGTGGGAAG SEQ ID NO:849	-7.9	-25.3	74	-17.4	0	-3.6
58	GCTCTTCATGTTTCCCAGCT SEQ ID NO:850	-7.9	-28.4	81.7	-20.5	0	-4.7
61	GACGCTCTTCATGTTTCCCA SEQ ID NO:851	-7.9	-27.3	76.4	-19.4	0	-4.7
165	CTTTTGCACTCACTGCTGTC SEQ ID NO:852	-7.9	-25.3	74.9	-16.1	-1.2	-5
216	ACTCGGCAGCAGCCACAGTC SEQ ID NO:853	-7.9	-29.5	82	-18.4	-3.2	-9.8
351	TCTTTGCAGATACCAAACTC SEQ ID NO:854	-7.9	-21.3	63.3	-12.8	-0.3	-5.2
493	AGAAACAAATCTGTTGGAAG SEQ ID NO:855	-7.9	-16.4	52.1	-6.9	-1.5	-5
495	AGAGAAACAAATCTGTTGGA SEQ ID NO:856	-7.9	-17.7	55.1	-8.7	-1	-4.4

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
548	CAACTTCTTCTCTCACAATA SEQ ID NO:857	-7.9	-20.2	61.9	-12.3	0	-1.2
554	CTTTCACAACTTCTTCTCTC SEQ ID NO:858	-7.9	-22	67.8	-14.1	0	-0.7
1493	TTATTCTAACCATTTTCAAC SEQ ID NO:859	-7.9	-18	56.4	-10.1	0	-1.2
1514	ACCTTATAGAGTCATAGGTT SEQ ID NO:860	-7.9	-21.7	66.7	-13.1	-0.5	-5.7
1988	TTTTTATTGAACAATAATAA SEQ ID NO:861	-7.9	-12.3	44.2	-3.5	-0.6	-9
62	AGACGCTCTTCATGTTTCCC SEQ ID NO:862	-7.8	-26.6	75.7	-18.8	0	-6
668	AAATGTTGGCTGTGTGTTGA SEQ ID NO:863	-7.8	-22.1	66.1	-14.3	0	-3.7
748	TTGTTTTCTGGATCCACCAT SEQ ID NO:864	-7.8	-24.7	71.4	-15.5	-1.2	-9.7
885	ATTACCTAAATTGCATTTTT SEQ ID NO:865	-7.8	-18.2	56.3	-10.4	0	-6.2
888	AAGATTACCTAAATTGCATT SEQ ID NO:866	-7.8	-17.8	54.9	-10	0	-5.3
1044	TTTATTTCCCACTCCCACCC SEQ ID NO:867	-7.8	-29.6	78.6	-21.8	0	-0.7
1246	TAACCCGGGAACTACATCAG SEQ ID NO:868	-7.8	-23.1	64.3	-13.9	-0.2	-10.7
1369	TACACACACAAACCACCAGT SEQ ID NO:869	-7.8	-22.9	64.3	-15.1	0	-2.6
1504	GTCATAGGTTTTTATTCTAA SEQ ID NO:870	-7.8	-18.9	60.5	-11.1	0	-2.6
1817	ATACTTCTGAGATATTTCCT SEQ ID NO:871	-7.8	-20.6	63.4	-12.8	0	-3.8
134	GGCAGTCCACCGCATAATTA SEQ ID NO:872	-7.7	-26.3	72.1	-17.7	-0.7	-5
465	ACTGAATATTGGAAGAAGGG SEQ ID NO:873	-7.7	-18.2	56	-10.5	0	-4.6
663	TTGGCTGTGTGTTGAACAAT SEQ ID NO:874	-7.7	-21.8	64.8	-13.2	-0.7	-7.8
879	TAAATTGCATTTTTAGTTCT SEQ ID NO:875	-7.7	-17.6	56.3	-9.9	0	-6.2
894	CCATGTAAGATTACCTAAAT SEQ ID NO:876	-7.7	-18.7	56.4	-11	0	-4.9
1125	TTGACTTTTCCCAAAGCCAA SEQ ID NO:877	-7.7	-23.6	65.8	-14.5	-1.3	-6.1
1227	GCAGCCTTTTGAAATTGCTC SEQ ID NO:878	-7.7	-23.9	68.9	-15.5	-0.4	-5.5
1229	CAGCAGCCTTTTGAAATTGC SEQ ID NO:879	-7.7	-23.3	66.9	-14.9	-0.4	-4.9
1630	ACAGCACTTATGTTTAAATA SEQ ID NO:880	-7.7	-17.7	55.8	-10	0	-5.4
1838	AAGTTCTTCACTTCAAATAA SEQ ID NO:881	-7.7	-17	54.4	-8.4	-0.7	-3.3
1943	ACAGCTTATGCAGCTTTACA SEQ ID NO:882	-7.7	-23.4	69.3	-13.7	-2	-6.9
120	TAATTATTGCTCCAGGCGGC SEQ ID NO:883	-7.6	-25.5	71.3	-16.4	-1.4	-7.2
152	TGCTGTCACAGTGTTGAGGG SEQ ID NO:884	-7.6	-25.4	75.6	-17.1	-0.4	-5.7
214	TCGGCAGCAGCCACAGTCGT SEQ ID NO:885	-7.6	-30.4	82.5	-19.6	-3.2	-9.8
344	AGATACCAAACTCTTCACCA SEQ ID NO:886	-7.6	-22.3	64.4	-14.7	0	-2.6

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
345	CAGATACCAAACTCTTCACC SEQ ID NO:887	-7.6	-22.3	64.4	-14.7	0	-2.6
645	ATCACGAAAATAGAGCCTTC SEQ ID NO:888	-7.6	-20.1	59.4	-12.5	0	-3.5
828	TCTACATGCATTCGAATATT SEQ ID NO:889	-7.6	-19.4	58.8	-11.2	0	-8.4
1754	CAAATATACTCCTAATTCCA SEQ ID NO:890	-7.6	-19.3	57.7	-11.7	0	-2.9
1849	AATTCTTAAATAAGTTCTTC SEQ ID NO:891	-7.6	-15.2	51.1	-7.6	0	-4.9
299	GACACCTCAGCCCCGGGCCA SEQ ID NO:892	-7.5	-35.2	87.6	-25.8	-1.8	-11.2
549	ACAACTTCTTCTCTCACAAT SEQ ID NO:893	-7.5	-20.7	63	-13.2	0	-0.9
665	TGTTGGCTGTGTGTTGAACA SEQ ID NO:894	-7.5	-23.7	70.3	-15.5	-0.5	-5.8
703	TTACATGTACTTATGCTATA SEQ ID NO:895	-7.5	-18.6	58.7	-10.6	0	-7.7
829	ATCTACATGCATTCGAATAT SEQ ID NO:896	-7.5	-19.3	58.5	-11.2	0	-8.4
1284	GTGTTTCCTATGCCCCAGAA SEQ ID NO:897	-7.5	-28	76.8	-20.5	0	-3
1524	ATGTTTGAAAACCTTATAGA SEQ ID NO:898	-7.5	-17.1	53.9	-9.1	-0.1	-5.7
1835	TTCTTCACTTCAAATAAAAT SEQ ID NO:899	-7.5	-15.1	49.8	-7.6	0	-1.2
1942	CAGCTTATGCAGCTTTACAT SEQ ID NO:900	-7.5	-23.2	68.6	-13.7	-2	-6.9
40	CTGCCTCCGGCTCGGCTCTC SEQ ID NO:901	-7.4	-33.5	88.7	-24	-2.1	-10
130	GTCCACCGCATAATTATTGC SEQ ID NO:902	-7.4	-24.5	68.5	-16.4	-0.4	-7.5
251	TGCGGTAGCAAGTTTCTCCC SEQ ID NO:903	-7.4	-27.6	77.3	-18.6	-1.6	-5.1
350	CTTTGCAGATACCAAACTCT SEQ ID NO:904	-7.4	-21.8	63.7	-13.8	-0.3	-5.2
388	CTCTCTGCAATCCATCCCGA SEQ ID NO:905	-7.4	-28.2	75.9	-20.8	0	-4.7
432	TTTCCCGTCCCCCTGTCACA SEQ ID NO:906	-7.4	-33.1	85.5	-25.7	0	-2.5
642	ACGAAAATAGAGCCTTCTCT SEQ ID NO:907	-7.4	-21.2	61.9	-12.2	-1.5	-6.5
728	GCATCACAATTTGGATCTTC SEQ ID NO:908	-7.4	-21.6	65.1	-14.2	0	-5.4
752	CTTTTTGTTTTCTGGATCCA SEQ ID NO:909	-7.4	-23	69	-14.7	0	-9.6
881	CCTAAATTGCATTTTTAGTT SEQ ID NO:910	-7.4	-19.2	58.8	-10.6	-0.9	-9.6
889	TAAGATTACCTAAATTGCAT SEQ ID NO:911	-7.4	-17.4	54.1	-10	0	-5.3
899	TGTCTCCATGTAAGATTACC SEQ ID NO:912	-7.4	-22.4	66.6	-15	0	-5.5
1002	TAAGTCTTCATTCCATATCC SEQ ID NO:913	-7.4	-22	66.3	-14.6	0	-2.7
1121	CTTTTCCCAAAGCCAAAAAA SEQ ID NO:914	-7.4	-19.9	56.8	-11.8	-0.4	-3.4
1235	CTACATCAGCAGCCTTTTGA SEQ ID NO:915	-7.4	-24.7	71.6	-17.3	0	-4.5
1364	ACACAAACCACCAGTGGGTA SEQ ID NO:916	-7.4	-24.7	68.7	-16	-1.2	-9

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1367	CACACACAAACCACCAGTGG SEQ ID NO:917	-7.4	-24.2	66.6	-15.8	-0.9	-8.5
1614	AATAAGGTCCCTCTGTTGCT SEQ ID NO:918	-7.4	-25.3	72.6	-17.9	0	-4.7
1622	TATGTTTAAATAAGGTCCCT SEQ ID NO:919	-7.4	-20.1	60.3	-12.7	0	-5.1
1636	GAAGTCACAGCACTTATGTT SEQ ID NO:920	-7.4	-21.8	66.1	-13.7	-0.5	-4.6
1723	AAGTTGACATGTTTTCTGCT SEQ ID NO:921	-7.4	-21.6	65.9	-14.2	0	-7.1
1960	TTTTAAAACAAAACCTAACA SEQ ID NO:922	-7.4	-13.7	46.1	-5.8	-0.1	-6
42	AGCTGCCTCCGGCTCGGCTC SEQ ID NO:923	-7.3	-34	89.6	-24.3	-2.4	-10
358	GGGACAGTCTTTGCAGATAC SEQ ID NO:924	-7.3	-23.6	70.6	-15.8	-0.2	-6
550	CACAACTTCTTCTCTCACAA SEQ ID NO:925	-7.3	-21.4	64.3	-14.1	0	-0.6
570	GACCCGGCAGCATTCTCTTT SEQ ID NO:926	-7.3	-28.7	78.6	-21.4	0	-6.3
626	CTCTCAGAAATCACAGCCGG SEQ ID NO:927	-7.3	-24.3	68.2	-17	0	-6.2
883	TACCTAAATTGCATTTTTAG SEQ ID NO:928	-7.3	-17.8	55.6	-9.6	-0.6	-9.2
901	CCTGTCTCCATGTAAGATTA SEQ ID NO:929	-7.3	-23.1	68	-15.8	0	-5.5
1228	AGCAGCCTTTTGAAATTGCT SEQ ID NO:930	-7.3	-23.5	67.6	-14.9	-1.2	-6.2
1336	CTTAGATTTATCTCTGAGGT SEQ ID NO:931	-7.3	-20.8	65.2	-12.6	-0.7	-6.2
1503	TCATAGGTTTTTATTCTAAC SEQ ID NO:932	-7.3	-17.9	57.8	-10.6	0	-2.7
1761	ATTCTTTCAAATATACTCCT SEQ ID NO:933	-7.3	-19.1	59.1	-11.8	0	-2.7
1776	CCTGTTTGTGCTAAGATTCT SEQ ID NO:934	-7.3	-23.2	69	-15.9	0	-3.8
1816	TACTTCTGAGATATTTCCTA SEQ ID NO:935	-7.3	-20.3	62.8	-13	0	-3.8
1844	TTAAATAAGTTCTTCACTTC SEQ ID NO:936	-7.3	-16.8	54.8	-8.4	-1	-4.2
1910	CACACACATTCACAACTCTG SEQ ID NO:937	-7.3	-21.2	62.7	-13.9	0	-1.8
336	AACTCTTCACCAAAAGGATC SEQ ID NO:938	-7.2	-19.9	59.5	-12.7	0	-4.1
547	AACTTCTTCTCTCACAATAT SEQ ID NO:939	-7.2	-19.5	60.6	-12.3	0	-2.4
583	CCTCATTACGGGAGACCCGG SEQ ID NO:940	-7.2	-28.6	74.5	-17.7	-3.7	-11
742	TCTGGATCCACCATGCATCA SEQ ID NO:941	-7.2	-26.7	74.7	-18.1	-1.2	-9.7
880	CTAAATTGCATTTTTAGTTC SEQ ID NO:942	-7.2	-17.6	56.3	-9.6	-0.4	-8.8
902	ACCTGTCTCCATGTAAGATT SEQ ID NO:943	-7.2	-23.6	69.2	-16.4	0	-5
1080	TCTAGAGAAGCTACCTACCA SEQ ID NO:944	-7.2	-23.6	68.5	-16.4	0	-5.2
1326	TCTCTGAGGTGGCATACGTT SEQ ID NO:945	-7.2	-25.3	73.8	-17.5	-0.3	-6.5
1587	TGACATTTTTTGAAATCCAG SEQ ID NO:946	-7.2	-18.3	56.4	-10.1	-0.9	-4.9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1991	TCTTTTTTATTGAACAATAA SEQ ID NO:947	-7.2	-14.7	49.4	-6.7	-0.4	-8.7
283	GCCACACTTCATGCCATCCA SEQ ID NO:948	-7.1	-29.3	79.1	-22.2	0	-4.4
314	CCCCATTAGAAGGCTGACAC SEQ ID NO:949	-7.1	-26	71.3	-18.9	0	-3.7
359	AGGGACAGTCTTTGCAGATA SEQ ID NO:950	-7.1	-23.4	70.3	-15.8	-0.2	-6
360	TAGGGACAGTCTTTGCAGAT SEQ ID NO:951	-7.1	-23.4	70.3	-15.8	-0.2	-6
369	AAGGTGCCGTAGGGACAGTC SEQ ID NO:952	-7.1	-26.7	75.9	-18	-1.5	-7.9
524	CATCTCCAGATGCCATGTCA SEQ ID NO:953	-7.1	-26.5	75.2	-18.7	-0.5	-6.9
753	ACTTTTTGTTTTCTGGATCC SEQ ID NO:954	-7.1	-22.5	68.4	-14.9	0	-7.5
862	TCTTCAGTGTTACTATACAC SEQ ID NO:955	-7.1	-20.3	64	-11.9	-1.2	-5.2
952	TAATTTGACTCACTGCGGTC SEQ ID NO:956	-7.1	-22.5	66.2	-14.9	-0.1	-6.2
1014	TTCTCCTGCTCTTAAGTCTT SEQ ID NO:957	-7.1	-24.4	73.7	-17.3	0	-6
1327	ATCTCTGAGGTGGCATACGT SEQ ID NO:958	-7.1	-25.2	73.4	-17.5	-0.3	-6.5
1721	GTTGACATGTTTTCTGCTGA SEQ ID NO:959	-7.1	-22.9	69.3	-15.8	0	-7.1
1837	AGTTCTTCACTTCAAATAAA SEQ ID NO:960	-7.1	-17	54.4	-9.9	0	-2.3
59	CGCTCTTCATGTTTCCCAGC SEQ ID NO:961	-7	-28.3	79.2	-21.3	0	-4.7
132	CAGTCCACCGCATAATTATT SEQ ID NO:962	-7	-23.4	66	-16.4	0	-5.6
231	CGCCCTGCAGCGCACACTCG SEQ ID NO:963	-7	-32.3	80.9	-23.9	-1.2	-10.1
702	TACATGTACTTATGCTATAT SEQ ID NO:964	-7	-18.5	58.3	-11.5	0	-7.3
810	TTTAACAAACACATACAAGT SEQ ID NO:965	-7	-15.6	50.4	-8.6	0	-2.8
1197	GCTGTTTGTTACTCAAATTT SEQ ID NO:966	-7	-20.1	61.9	-11.5	-1.6	-6.5
1223	CCTTTTGAAATTGCTCTCAG SEQ ID NO:967	-7	-21.6	64	-14.6	0	-3.6
1408	ACACATTTATTTATAAAAAT SEQ ID NO:968	-7	-12.5	44.4	-4.8	-0.4	-6.5
1508	TAGAGTCATAGGTTTTTATT SEQ ID NO:969	-7	-18.9	61	-11.9	0	-4.8
1613	ATAAGGTCCCTCTGTTGCTC SEQ ID NO:970	-7	-26.4	76.9	-19.4	0	-4.7
1624	CTTATGTTTAAATAAGGTCC SEQ ID NO:971	-7	-18.2	56.9	-10.4	-0.6	-5.6
1762	GATTCTTTCAAATATACTCC SEQ ID NO:972	-7	-18.8	58.4	-11.8	0	-2.7
1772	TTTGTGCTAAGATTCTTTCA SEQ ID NO:973	-7	-20.4	63.4	-12.9	-0.1	-5.6
1941	AGCTTATGCAGCTTTACATT SEQ ID NO:974	-7	-22.6	67.8	-13.7	-1.9	-6.9
273	ATGCCATCCATGCCTGAGAC SEQ ID NO:975	-6.9	-27.7	75.8	-20.8	0	-4.2
354	CAGTCTTTGCAGATACCAAA SEQ ID NO:976	-6.9	-21.7	63.9	-14.3	-0.2	-5.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
355	ACAGTCTTTGCAGATACCAA SEQ ID NO:977	-6.9	-22.6	66.6	-15.2	-0.2	-5.2
551	TCACAACTTCTTCTCTCACA SEQ ID NO:978	-6.9	-22.5	68.1	-15.6	0	-0.6
639	AAAATAGAGCCTTCTCTCAG SEQ ID NO:979	-6.9	-20.7	62.4	-12.3	-1.4	-5.1
662	TGGCTGTGTGTTGAACAATC SEQ ID NO:980	-6.9	-22.1	66	-14.3	-0.7	-7.8
704	ATTACATGTACTTATGCTAT SEQ ID NO:981	-6.9	-18.9	59.3	-11.5	0	-7.7
1616	TAAATAAGGTCCCTCTGTTG SEQ ID NO:982	-6.9	-21.6	63.7	-14.7	0	-4.7
1632	TCACAGCACTTATGTTTAAA SEQ ID NO:983	-6.9	-19.1	58.9	-12.2	0	-5.2
1664	TTTTCATACCTTAAATTGAA SEQ ID NO:984	-6.9	-16.6	52.8	-9.2	-0.1	-3.6
1800	CCTAAGAACATCTAGTACAA SEQ ID NO:985	-6.9	-18.8	57.5	-11.9	0	-5.7
447	GGGAATTTCAGGCATTTTCC SEQ ID NO:986	-6.8	-24	69.9	-16.3	-0.8	-5
449	AGGGGAATTTCAGGCATTTT SEQ ID NO:987	-6.8	-22.8	67.5	-16	0	-5
525	CCATCTCCAGATGCCATGTC SEQ ID NO:988	-6.8	-27.8	77.7	-19.9	-1	-7.8
830	AATCTACATGCATTCGAATA SEQ ID NO:989	-6.8	-18.6	56.7	-11.2	0	-8.4
835	TAACAAATCTACATGCATTC SEQ ID NO:990	-6.8	-17.4	54.6	-10.6	0	-6.7
988	ATATCCCAACATTAATGTAC SEQ ID NO:991	-6.8	-19.2	57.9	-11.1	-0.2	-10.5
1629	CAGCACTTATGTTTAAATAA SEQ ID NO:992	-6.8	-16.8	53.5	-10	0	-5.4
1722	AGTTGACATGTTTTCTGCTG SEQ ID NO:993	-6.8	-22.3	68.1	-15.5	0	-6.5
263	TGCCTGAGACTGTGCGGTAG SEQ ID NO:994	-6.7	-26.9	75.7	-19.6	-0.3	-5.4
298	ACACCTCAGCCCCGGGCCAC SEQ ID NO:995	-6.7	-34.8	87	-26.2	-1.8	-11.2
300	TGACACCTCAGCCCCGGGCC SEQ ID NO:996	-6.7	-34.5	86.5	-25.9	-1.8	-11.3
401	GGCAGTTGCAGGTCTCTCTG SEQ ID NO:997	-6.7	-27.8	83.1	-20.2	-0.7	-6.6
751	TTTTTGTTTTCTGGATCCAC SEQ ID NO:998	-6.7	-22.3	67.6	-14.7	0	-9.7
817	TCGAATATTTAACAAACACA SEQ ID NO:999	-6.7	-15.3	49.3	-8.6	0	-4.8
1666	TATTTTCATACCTTAAATTG SEQ ID NO:1000	-6.7	-16.4	52.8	-9.7	0	-3.2
1756	TTCAAATATACTCCTAATTC SEQ ID NO:1001	-6.7	-17.1	54.4	-10.4	0	-2.9
1986	TTTATTGAACAATAATAAAC SEQ ID NO:1002	-6.7	-11.6	42.7	-3.5	-1.3	-9
183	CTCTTGCAGCGCGGGCTGCT SEQ ID NO:1003	-6.6	-31.8	84.7	-19.7	-5.5	-15.6
294	CTCAGCCCCGGGCCACACTT SEQ ID NO:1004	-6.6	-33.6	85.4	-25.1	-1.8	-11.2
523	ATCTCCAGATGCCATGTCAT SEQ ID NO:1005	-6.6	-25.8	74	-18.7	-0.1	-4.3
1150	TCAGGGGTTTTCTGGTTGTT SEQ ID NO:1006	-6.6	-25.3	76.8	-17.8	-0.7	-4.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
1233	ACATCAGCAGCCTTTTGAAA SEQ ID NO:1007	-6.6	-22.7	65.7	-16.1	0	-4.5
1291	AGTGTATGTGTTTCCTATGC SEQ ID NO:1008	-6.6	-23.5	71.8	-16.9	0	-2.6
1318	GTGGCATACGTTAAAGCTAT SEQ ID NO:1009	-6.6	-21.6	63.4	-14.3	-0.4	-5.1
1370	ATACACACACAAACCACCAG SEQ ID NO:1010	-6.6	-21.7	61.5	-15.1	0	-0.9
1488	CTAACCATTTTCAACAAATA SEQ ID NO:1011	-6.6	-16.7	52.3	-9.6	-0.1	-2.7
1726	TTAAAGTTGACATGTTTTCT SEQ ID NO:1012	-6.6	-18	57.3	-11.4	0	-7.1
1966	ATGTCCTTTTAAAACAAAAC SEQ ID NO:1013	-6.6	-15.4	49.8	-8.2	-0.3	-6.2
217	CACTCGGCAGCAGCCACAGT SEQ ID NO:1014	-6.5	-29.8	81.2	-20.6	-2.7	-9.3
451	GAAGGGGAATTTCAGGCATT SEQ ID NO:1015	-6.5	-22.5	65.8	-16	0	-5
638	AAATAGAGCCTTCTCTCAGA SEQ ID NO:1016	-6.5	-22	65.9	-13.8	-1.7	-5.1
827	CTACATGCATTCGAATATTT SEQ ID NO:1017	-6.5	-19.1	57.9	-12	0	-8.4
836	TTAACAAATCTACATGCATT SEQ ID NO:1018	-6.5	-17.1	53.7	-10.6	0	-6.7
837	TTTAACAAATCTACATGCAT SEQ ID NO:1019	-6.5	-17.1	53.7	-10.6	0	-6.4
1216	AAATTGCTCTCAGTTCAAAG SEQ ID NO:1020	-6.5	-18.8	58.3	-12.3	0	-3.2
1325	CTCTGAGGTGGCATACGTTA SEQ ID NO:1021	-6.5	-24.6	71.5	-17.5	-0.3	-5.2
1363	CACAAACCACCAGTGGGTAA SEQ ID NO:1022	-6.5	-23.8	66.1	-16	-1.2	-9
1757	TTTCAAATATACTCCTAATT SEQ ID NO:1023	-6.5	-16.8	53.5	-10.3	0	-2.7
1845	CTTAAATAAGTTCTTCACTT SEQ ID NO:1024	-6.5	-17.3	55.4	-9.9	-0.8	-4.2
1899	ACAACTCTGTTGGCCAACTT SEQ ID NO:1025	-6.5	-24.1	68.8	-14.2	-1.8	-15
1987	TTTTATTGAACAATAATAAA SEQ ID NO:1026	-6.5	-11.5	42.5	-3.5	-1.4	-9
73	GGTCAGCAGCAAGACGCTCT SEQ ID NO:1027	-6.4	-27.4	77.5	-19.5	-1.4	-8.5
430	TCCCGTCCCCCTGTCACAGA SEQ ID NO:1028	-6.4	-33.5	86.4	-26.5	-0.3	-5.2
459	TATTGGAAGAAGGGGAATTT SEQ ID NO:1029	-6.4	-18.5	56.7	-12.1	0	-3.3
808	TAACAAACACATACAAGTGT SEQ ID NO:1030	-6.4	-16.6	52.4	-8.6	-1.6	-6
890	GTAAGATTACCTAAATTGCA SEQ ID NO:1031	-6.4	-18.6	56.9	-12.2	0	-5.3
1056	AGGGCTAAATATTTTATTTC SEQ ID NO:1032	-6.4	-17.7	56.3	-10.5	-0.6	-8.2
1062	CAAGGAAGGGCTAAATATTT SEQ ID NO:1033	-6.4	-18.4	56.1	-12	0	-6.4
1142	TTTCTGGTTGTTTTATTTTG SEQ ID NO:1034	-6.4	-19.5	62.1	-13.1	0	-1.5
1410	TAACACATTTATTTATAAAA SEQ ID NO:1035	-6.4	-12.2	43.9	-4.8	-0.9	-6.5
1549	GGATAATAAATTTATCATGC SEQ ID NO:1036	-6.4	-15.9	51.5	-6.9	-2.6	-7.6

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1634	AGTCACAGCACTTATGTTTA SEQ ID NO:1037	-6.4	-21.7	66.8	-15.3	0	-4.1
1688	TTTTACAAACCTCCTAAAAA SEQ ID NO:1038	-6.4	-16.8	52	-10.4	0	-3.2
1917	GGCCTTCCACACACATTCAC SEQ ID NO:1039	-6.4	-27.2	75.7	-20.3	-0.2	-6.4
131	AGTCCACCGCATAATTATTG SEQ ID NO:1040	-6.3	-22.7	64.8	-16.4	0	-5.6
460	ATATTGGAAGAAGGGGAATT SEQ ID NO:1041	-6.3	-18.4	56.4	-12.1	0	-3.1
637	AATAGAGCCTTCTCTCAGAA SEQ ID NO:1042	-6.3	-22	65.9	-14	-1.7	-6.3
816	CGAATATTTAACAAACACAT SEQ ID NO:1043	-6.3	-14.9	48.3	-8.6	0	-4.8
1081	TTCTAGAGAAGCTACCTACC SEQ ID NO:1044	-6.3	-23	67.7	-16.7	0	-5.8
1198	AGCTGTTTGTTACTCAAATT SEQ ID NO:1045	-6.3	-20	61.8	-12.5	-1.1	-9.3
1379	TTTACCTTCATACACACACA SEQ ID NO:1046	-6.3	-21.5	63.6	-15.2	0	-0.9
1434	ATGGGTAGGGAAGATGACTT SEQ ID NO:1047	-6.3	-22	65.5	-15	-0.5	-3.2
1435	TATGGGTAGGGAAGATGACT SEQ ID NO:1048	-6.3	-21.6	64.6	-15.3	0	-2.1
1635	AAGTCACAGCACTTATGTTT SEQ ID NO:1049	-6.3	-21.3	65	-15	0	-4.3
1637	CGAAGTCACAGCACTTATGT SEQ ID NO:1050	-6.3	-22.5	66	-15.5	-0.5	-4.6
1689	CTTTTACAAACCTCCTAAAA SEQ ID NO:1051	-6.3	-18.4	55.3	-12.1	0	-3.2
1944	AACAGCTTATGCAGCTTTAC SEQ ID NO:1052	-6.3	-22	65.7	-13.7	-2	-6.9
60	ACGCTCTTCATGTTTCCCAG SEQ ID NO:1053	-6.2	-26.7	75.4	-20.5	0	-4.7
97	CAGGTGTGCAGGCACGAGGA SEQ ID NO:1054	-6.2	-27.9	77.9	-19.2	-2.5	-10
384	CTGCAATCCATCCCGAAGGT SEQ ID NO:1055	-6.2	-27.3	72.8	-19.8	-1.2	-7.1
566	CGGCAGCATTCTCTTTCACA SEQ ID NO:1056	-6.2	-25.9	74.1	-19.7	0	-5.3
813	ATATTTAACAAACACATACA SEQ ID NO:1057	-6.2	-14.8	48.8	-8.6	0	-2.4
1208	CTCAGTTCAAAGCTGTTTGT SEQ ID NO:1058	-6.2	-22.3	67.8	-14.6	-1.4	-6.8
1251	ACAGGTAACCCGGGAACTAC SEQ ID NO:1059	-6.2	-24.6	67.6	-16.8	-1.1	-11
45	CCCAGCTGCCTCCGGCTCGG SEQ ID NO:1060	-6.1	-35.6	88.8	-27.1	-2.4	-10.5
46	TCCCAGCTGCCTCCGGCTCG SEQ ID NO:1061	-6.1	-34.8	88.3	-26.6	-2.1	-8.2
69	AGCAGCAAGACGCTCTTCAT SEQ ID NO:1062	-6.1	-25.1	71.8	-17.7	-1.2	-6
133	GCAGTCCACCGCATAATTAT SEQ ID NO:1063	-6.1	-25.1	69.6	-19	0	-5.6
284	GGCCACACTTCATGCCATCC SEQ ID NO:1064	-6.1	-29.8	80.6	-22.2	-1.4	-7.6
403	CTGGCAGTTGCAGGTCTCTC SEQ ID NO:1065	-6.1	-27.8	83.1	-20.8	-0.7	-6.6
462	GAATATTGGAAGAAGGGGAA SEQ ID NO:1066	-6.1	-18.2	55.6	-12.1	0	-4.6

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
565	GGCAGCATTCTCTTTCACAA SEQ ID NO:1067	-6.1	-24.4	71.7	-18.3	0	-5.3
809	TTAACAAACACATACAAGTG SEQ ID NO:1068	-6.1	-15.5	50.1	-8.6	-0.6	-4.7
818	TTCGAATATTTAACAAACAC SEQ ID NO:1069	-6.1	-14.7	48.4	-8.6	0	-6.2
1055	GGGCTAAATATTTTATTTCC SEQ ID NO:1070	-6.1	-19.7	60	-12.9	-0.4	-8.2
1285	TGTGTTTCCTATGCCCCAGA SEQ ID NO:1071	-6.1	-28.7	79.2	-22.6	0	-3
1332	GATTTATCTCTGAGGTGGCA SEQ ID NO:1072	-6.1	-23.8	71.5	-17.7	0	-6.2
1362	ACAAACCACCAGTGGGTAAA SEQ ID NO:1073	-6.1	-22.4	63.1	-15.1	-1.1	-8.2
1407	CACATTTATTTATAAAAATA SEQ ID NO:1074	-6.1	-12	43.5	-4.8	-1	-6.5
1586	GACATTTTTTGAAATCCAGA SEQ ID NO:1075	-6.1	-18.9	57.7	-11.8	-0.9	-4.3
1773	GTTTGTGCTAAGATTCTTTC SEQ ID NO:1076	-6.1	-20.9	65.5	-14.8	0	-5.6
1922	TCAAAGGCCTTCCACACACA SEQ ID NO:1077	-6.1	-25.5	70.4	-18.1	-0.2	-10.6
13	GGTCTTTGCTGGTGGGAAGC SEQ ID NO:1078	-6	-27.1	78.8	-20.3	-0.6	-5.1
63	AAGACGCTCTTCATGTTTCC SEQ ID NO:1079	-6	-23.9	69.6	-17.2	-0.4	-6.8
429	CCCGTCCCCCTGTCACAGAT SEQ ID NO:1080	-6	-33.1	84.5	-26.5	-0.3	-5.2
450	AAGGGGAATTTCAGGCATTT SEQ ID NO:1081	-6	-22	64.9	-16	0	-4.2
569	ACCCGGCAGCATTCTCTTTC SEQ ID NO:1082	-6	-28.5	79.1	-22.5	0	-6.3
648	ACAATCACGAAAATAGAGCC SEQ ID NO:1083	-6	-18.9	56	-12.9	0	-3.5
1049	AATATTTTATTTCCCACTCC SEQ ID NO:1084	-6	-21.8	64	-15.8	0	-3.8
1190	GTTACTCAAATTTCCATAAG SEQ ID NO:1085	-6	-18.1	56.4	-12.1	0	-4.5
1249	AGGTAACCCGGGAACTACAT SEQ ID NO:1086	-6	-24.4	67.1	-16.8	-1.1	-11
1409	AACACATTTATTTATAAAAA SEQ ID NO:1087	-6	-11.8	43	-4.8	-0.9	-6.5
1657	ACCTTAAATTGAAAATTCAC SEQ ID NO:1088	-6	-15.5	50	-8.2	-1.2	-5.7
1758	CTTTCAAATATACTCCTAAT SEQ ID NO:1089	-6	-17.6	55	-11.6	0	-2.7
337	AAACTCTTCACCAAAAGGAT SEQ ID NO:1090	-5.9	-18.8	56.4	-12.9	0	-3.7
342	ATACCAAACTCTTCACCAAA SEQ ID NO:1091	-5.9	-20.3	59.1	-14.4	0	-0.9
545	CTTCTTCTCTCACAATATTG SEQ ID NO:1092	-5.9	-20.1	62.5	-13.7	0	-8.2
972	GTACATCAAAGTCAAAGAAC SEQ ID NO:1093	-5.9	-16.5	52.8	-10.6	0	-4.6
974	ATGTACATCAAAGTCAAAGA SEQ ID NO:1094	-5.9	-17	54	-10.6	0	-7.6
1120	TTTTCCCAAAGCCAAAAAAA SEQ ID NO:1095	-5.9	-18.3	53.6	-12.4	0	-3.2
1124	TGACTTTTCCCAAAGCCAAA SEQ ID NO:1096	-5.9	-22.8	63.5	-15.5	-1.3	-5.3

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1224	GCCTTTTGAAATTGCTCTCA SEQ ID NO:1097	-5.9	-23.4	67.9	-17.5	0	-3.9
1371	CATACACACACAAACCACCA SEQ ID NO:1098	-5.9	-22.4	62.4	-16.5	0	-0.9
1617	TTAAATAAGGTCCCTCTGTT SEQ ID NO:1099	-5.9	-21.7	64.2	-15.8	0	-4.7
1809	GAGATATTTCCTAAGAACAT SEQ ID NO:1100	-5.9	-18.2	56.5	-11.8	-0.2	-4
1810	TGAGATATTTCCTAAGAACA SEQ ID NO:1101	-5.9	-18.2	56.5	-11.8	-0.2	-4.6
1889	TGGCCAACTTCAAGAATAAA SEQ ID NO:1102	-5.9	-18.8	56.1	-12.4	0	-8.3
293	TCAGCCCCGGGCCACACTTC SEQ ID NO:1103	-5.8	-33.1	85.4	-25.4	-1.8	-11.2
297	CACCTCAGCCCCGGGCCACA SEQ ID NO:1104	-5.8	-35.3	87.2	-27.6	-1.8	-11.2
811	ATTTAACAAACACATACAAG SEQ ID NO:1105	-5.8	-14.4	47.9	-8.6	0	-2.4
893	CATGTAAGATTACCTAAATT SEQ ID NO:1106	-5.8	-16.8	53.1	-11	0	-4.9
1061	AAGGAAGGGCTAAATATTTT SEQ ID NO:1107	-5.8	-17.8	55.2	-12	0	-6.6
1207	TCAGTTCAAAGCTGTTTGTT SEQ ID NO:1108	-5.8	-21.5	66.1	-14.2	-1.4	-6.8
1230	TCAGCAGCCTTTTGAAATTG SEQ ID NO:1109	-5.8	-21.9	64.3	-16.1	0	-4.5
1463	AGATTTCTTTCCTCAAGAGG SEQ ID NO:1110	-5.8	-21.8	66.2	-15.2	-0.6	-7.9
1662	TTCATACCTTAAATTGAAAA SEQ ID NO:1111	-5.8	-15	49	-9.2	0	-3.5
1746	CTCCTAATTCCACCTATATT SEQ ID NO:1112	-5.8	-23	66.2	-17.2	0	-2.6
1829	ACTTCAAATAAAATACTTCT SEQ ID NO:1113	-5.8	-14.7	49	-8.9	0	-1.2
1945	TAACAGCTTATGCAGCTTTA SEQ ID NO:1114	-5.8	-21.5	64.6	-13.7	-2	-6.9
1962	CCTTTTAAAACAAAACCTAA SEQ ID NO:1115	-5.8	-15.7	49.5	-9.3	-0.3	-6.2
1963	TCCTTTTAAAACAAAACCTA SEQ ID NO:1116	-5.8	-16.8	52	-10.4	-0.3	-6.2
1	TGGGAAGCAGCCGTGACCCA SEQ ID NO:1117	-5.7	-30.1	78.4	-22.5	-1.9	-6.9
385	TCTGCAATCCATCCCGAAGG SEQ ID NO:1118	-5.7	-26.5	71.2	-19.8	-0.9	-6.7
452	AGAAGGGGAATTTCAGGCAT SEQ ID NO:1119	-5.7	-22.4	65.7	-16	-0.5	-5
646	AATCACGAAAATAGAGCCTT SEQ ID NO:1120	-5.7	-19	56.4	-13.3	0	-3.2
664	GTTGGCTGTGTGTTGAACAA SEQ ID NO:1121	-5.7	-23	68.1	-16.4	-0.7	-7.8
743	TTCTGGATCCACCATGCATC SEQ ID NO:1122	-5.7	-26.1	73.9	-19	-1.2	-9.7
973	TGTACATCAAAGTCAAAGAA SEQ ID NO:1123	-5.7	-16.3	52.2	-10.6	0	-5.9
1136	GTTGTTTTATTTTGACTTTT SEQ ID NO:1124	-5.7	-18.8	60.3	-13.1	0	-2.5
1210	CTCTCAGTTCAAAGCTGTTT SEQ ID NO:1125	-5.7	-22.4	68.2	-15.3	-1.3	-5.1
1317	TGGCATACGTTAAAGCTATT SEQ ID NO:1126	-5.7	-20.5	60.8	-14.1	-0.4	-5.1

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1509	ATAGAGTCATAGGTTTTTAT SEQ ID NO:1127	-5.7	-18.8	60.6	-13.1	0	-4.8
1621	ATGTTTAAATAAGGTCCCTC SEQ ID NO:1128	-5.7	-20.8	62.2	-15.1	0	-5.1
1633	GTCACAGCACTTATGTTTAA SEQ ID NO:1129	-5.7	-21	64.2	-15.3	0	-5.8
1661	TCATACCTTAAATTGAAAAT SEQ ID NO:1130	-5.7	-14.9	48.8	-9.2	0	-3.2
1663	TTTCATACCTTAAATTGAAA SEQ ID NO:1131	-5.7	-15.8	50.9	-9.2	-0.8	-4.3
1767	GCTAAGATTCTTTCAAATAT SEQ ID NO:1132	-5.7	-17.3	55	-11.6	0.6	-5.6
67	CAGCAAGACGCTCTTCATGT SEQ ID NO:1133	-5.6	-24.5	70.4	-17.6	-1.2	-6.9
206	AGCCACAGTCGTCGAGCACT SEQ ID NO:1134	-5.6	-28.4	78.4	-22.2	-0.3	-5.3
275	TCATGCCATCCATGCCTGAG SEQ ID NO:1135	-5.6	-28	76.7	-20.6	-1.8	-5
292	CAGCCCCGGGCCACACTTCA SEQ ID NO:1136	-5.6	-33.4	84.6	-25.9	-1.8	-11.2
669	AAAATGTTGGCTGTGTGTTG SEQ ID NO:1137	-5.6	-20.8	62.6	-15.2	0	-3.7
970	ACATCAAAGTCAAAGAACTA SEQ ID NO:1138	-5.6	-16.2	51.9	-10.6	0	-3
971	TACATCAAAGTCAAAGAACT SEQ ID NO:1139	-5.6	-16.2	51.9	-10.6	0	-2.9
1006	CTCTTAAGTCTTCATTCCAT SEQ ID NO:1140	-5.6	-22.2	67.5	-16.6	0	-6
1007	GCTCTTAAGTCTTCATTCCA SEQ ID NO:1141	-5.6	-24	72	-18.4	0	-6
1328	TATCTCTGAGGTGGCATACG SEQ ID NO:1142	-5.6	-23.7	69.4	-17.5	-0.3	-6.5
1690	TCTTTTACAAACCTCCTAAA SEQ ID NO:1143	-5.6	-19.5	58.2	-13.9	0	-2.3
1806	ATATTTCCTAAGAACATCTA SEQ ID NO:1144	-5.6	-18	56.4	-11.9	-0.2	-3.1
1830	CACTTCAAATAAAATACTTC SEQ ID NO:1145	-5.6	-14.5	48.4	-8.9	0	-1.2
1971	TAAACATGTCCTTTTAAAAC SEQ ID NO:1146	-5.6	-15.8	50.8	-10.2	0	-6.9
50	TGTTTCCCAGCTGCCTCCGG SEQ ID NO:1147	-5.5	-32.3	85.2	-26.3	0	-8.1
147	TCACAGTGTTGAGGGCAGTC SEQ ID NO:1148	-5.5	-25.6	77.3	-20.1	0	-6.5
458	ATTGGAAGAAGGGGAATTTC SEQ ID NO:1149	-5.5	-19.2	58.6	-13.7	0	-3.8
461	AATATTGGAAGAAGGGGAAT SEQ ID NO:1150	-5.5	-17.6	54.4	-12.1	0	-3.8
619	AAATCACAGCCGGGATCAGC SEQ ID NO:1151	-5.5	-25.1	69.5	-19.6	0	-6.9
812	TATTTAACAAACACATACAA SEQ ID NO:1152	-5.5	-14.1	47.3	-8.6	0	-2.4
1215	AATTGCTCTCAGTTCAAAGC SEQ ID NO:1153	-5.5	-21.3	64.5	-15.2	-0.3	-3.9
1329	TTATCTCTGAGGTGGCATAC SEQ ID NO:1154	-5.5	-23	69.7	-17.5	0	-6.2
1378	TTACCTTCATACACACACAA SEQ ID NO:1155	-5.5	-20.7	61.2	-15.2	0	-0.9
1406	ACATTTATTTATAAAAATAT SEQ ID NO:1156	-5.5	-11.3	42.2	-4.8	-0.9	-6.5

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1436	ATATGGGTAGGGAAGATGAC SEQ ID NO:1157	-5.5	-20.7	62.6	-15.2	0	-2
1744	CCTAATTCCACCTATATTTT SEQ ID NO:1158	-5.5	-21.9	63.6	-16.4	0	-2.9
1834	TCTTCACTTCAAATAAAATA SEQ ID NO:1159	-5.5	-14.7	49	-9.2	0	-1.2
1890	TTGGCCAACTTCAAGAATAA SEQ ID NO:1160	-5.5	-19.6	58.1	-13	0	-10.2
1921	CAAAGGCCTTCCACACACAT SEQ ID NO:1161	-5.5	-25.1	68.9	-18.1	-1	-10.6
47	TTCCCAGCTGCCTCCGGCTC SEQ ID NO:1162	-5.4	-34.1	89.5	-26.6	-2.1	-8.3
226	TGCAGCGCACACTCGGCAGC SEQ ID NO:1163	-5.4	-30.3	80.9	-23.6	-1.2	-8.5
622	CAGAAATCACAGCCGGGATC SEQ ID NO:1164	-5.4	-23.9	66.8	-18.5	0	-6.9
954	ACTAATTTGACTCACTGCGG SEQ ID NO:1165	-5.4	-22	64.1	-16.6	0	-4.7
955	AACTAATTTGACTCACTGCG SEQ ID NO:1166	-5.4	-20.1	59.7	-14.7	0	-4
1141	TTCTGGTTGTTTTATTTTGA SEQ ID NO:1167	-5.4	-20	63.2	-14.6	0	-2.1
1181	ATTTCCATAAGCTTCAAACA SEQ ID NO:1168	-5.4	-19.7	59.2	-14.3	0	-6.8
1234	TACATCAGCAGCCTTTTGAA SEQ ID NO:1169	-5.4	-23.1	67.4	-17.7	0	-4.5
1330	TTTATCTCTGAGGTGGCATA SEQ ID NO:1170	-5.4	-22.9	69.5	-17.5	0	-5.6
1553	TTATGGATAATAAATTTATC SEQ ID NO:1171	-5.4	-13.2	46.2	-6.9	-0.7	-8.1
1554	ATTATGGATAATAAATTTAT SEQ ID NO:1172	-5.4	-12.8	45.2	-6.8	-0.3	-7.9
1795	GAACATCTAGTACAACAGTC SEQ ID NO:1173	-5.4	-19.4	60.4	-14	0	-5.3
1898	CAACTCTGTTGGCCAACTTC SEQ ID NO:1174	-5.4	-24.3	69.8	-15.5	-0.9	-15
254	CTGTGCGGTAGCAAGTTTCT SEQ ID NO:1175	-5.3	-25.3	73.6	-18	-2	-5.6
282	CCACACTTCATGCCATCCAT SEQ ID NO:1176	-5.3	-27.5	74.9	-22.2	0	-4.4
521	CTCCAGATGCCATGTCATGC SEQ ID NO:1177	-5.3	-27.2	76.6	-21.9	0.3	-4.5
597	GGATTTAACCATTTCCTCAT SEQ ID NO:1178	-5.3	-22.5	65.6	-17.2	0	-3.4
660	GCTGTGTGTTGAACAATCAC SEQ ID NO:1179	-5.3	-21.8	65.2	-15.6	-0.8	-6.6
705	AATTACATGTACTTATGCTA SEQ ID NO:1180	-5.3	-18.2	57.2	-12.4	0	-7.7
831	AAATCTACATGCATTCGAAT SEQ ID NO:1181	-5.3	-18.2	55.4	-12.4	0	-8
1433	TGGGTAGGGAAGATGACTTG SEQ ID NO:1182	-5.3	-22	65.4	-15.8	-0.7	-3.1
1582	TTTTTTGAAATCCAGAGTGA SEQ ID NO:1183	-5.3	-19.2	59	-13.9	0	-3.3
1583	ATTTTTTGAAATCCAGAGTG SEQ ID NO:1184	-5.3	-18.6	57.7	-12.4	-0.7	-4.3
1667	TTATTTTCATACCTTAAATT SEQ ID NO:1185	-5.3	-16.5	53.1	-11.2	0	-2.9
1753	AAATATACTCCTAATTCCAC SEQ ID NO:1186	-5.3	-18.8	57.1	-13.5	0	-2.9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
1771	TTGTGCTAAGATTCTTTCAA SEQ ID NO:1187	-5.3	-19.6	60.8	-13.8	-0.1	-5.6
1804	ATTTCCTAAGAACATCTAGT SEQ ID NO:1188	-5.3	-19.5	60.2	-13.7	-0.2	-4.2
1850	TAATTCTTAAATAAGTTCTT SEQ ID NO:1189	-5.3	-14.5	49.3	-9.2	0	-4.3
1961	CTTTTAAAACAAAACCTAAC SEQ ID NO:1190	-5.3	-13.9	46.6	-8	-0.3	-6.2
1993	GTTCTTTTTTATTGAACAAT SEQ ID NO:1191	-5.3	-17	54.8	-10.2	-1.4	-5.5
304	AGGCTGACACCTCAGCCCCG SEQ ID NO:1192	-5.2	-32.2	83.1	-20.9	-6.1	-14
381	CAATCCATCCCGAAGGTGCC SEQ ID NO:1193	-5.2	-28.4	74.3	-21.9	-1.2	-6
617	ATCACAGCCGGGATCAGCGT SEQ ID NO:1194	-5.2	-28.5	77.2	-22.4	-0.7	-6.9
815	GAATATTTAACAAACACATA SEQ ID NO:1195	-5.2	-13.8	46.8	-8.6	0	-4.8
838	ATTTAACAAATCTACATGCA SEQ ID NO:1196	-5.2	-17.1	53.7	-11.9	0	-5.2
1151	TTCAGGGGTTTTCTGGTTGT SEQ ID NO:1197	-5.2	-25.3	76.8	-19.2	-0.7	-4.2
1670	AACTTATTTTCATACCTTAA SEQ ID NO:1198	-5.2	-17.5	55.2	-12.3	0	-2
1797	AAGAACATCTAGTACAACAG SEQ ID NO:1199	-5.2	-17.1	54.3	-11.9	0	-5.7
1929	TTTACATTCAAAGGCCTTCC SEQ ID NO:1200	-5.2	-23	66.5	-16.5	0	-10.6
48	TTTCCCAGCTGCCTCCGGCT SEQ ID NO:1201	-5.1	-33.8	88	-26.6	-2.1	-8.3
182	TCTTGCAGCGCGGGCTGCTT SEQ ID NO:1202	-5.1	-31	83.2	-19.7	-6.2	-16.3
573	GGAGACCCGGCAGCATTCTC SEQ ID NO:1203	-5.1	-29.4	80.1	-23.6	-0.5	-6.3
661	GGCTGTGTGTTGAACAATCA SEQ ID NO:1204	-5.1	-22.8	67.3	-17	-0.4	-4.9
1214	ATTGCTCTCAGTTCAAAGCT SEQ ID NO:1205	-5.1	-22.9	68.8	-16.6	-1.1	-4.8
1335	TTAGATTTATCTCTGAGGTG SEQ ID NO:1206	-5.1	-19.9	62.9	-13.9	-0.7	-6.2
159	CACTCACTGCTGTCACAGTG SEQ ID NO:1207	-5	-25.1	74	-17	-3.1	-9.1
208	GCAGCCACAGTCGTCGAGCA SEQ ID NO:1208	-5	-29.8	81.3	-24.2	-0.3	-4.9
230	GCCCTGCAGCGCACACTCGG SEQ ID NO:1209	-5	-32.7	83.8	-26.8	-0.7	-9.2
349	TTTGCAGATACCAAACTCTT SEQ ID NO:1210	-5	-21	62.2	-15.5	-0.1	-5.2
425	TCCCCCTGTCACAGATGCCT SEQ ID NO:1211	-5	-31.8	84.3	-26.8	0.2	-4.7
453	AAGAAGGGGAATTTCAGGCA SEQ ID NO:1212	-5	-21.7	63.6	-16	-0.5	-5
727	CATCACAATTTGGATCTTCA SEQ ID NO:1213	-5	-20.5	62.1	-15.5	0	-5.4
958	AAGAACTAATTTGACTCACT SEQ ID NO:1214	-5	-17.4	54.8	-12.4	0	-2.7
1333	AGATTTATCTCTGAGGTGGC SEQ ID NO:1215	-5	-23.1	70.6	-17.4	-0.5	-6.2
1692	CTTCTTTTACAAACCTCCTA SEQ ID NO:1216	-5	-21.9	64.2	-16.9	0	-1.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1818	AATACTTCTGAGATATTTCC SEQ ID NO:1217	-5	-19	59.3	-14	0	-3.8
54	TTCATGTTTCCCAGCTGCCT SEQ ID NO:1218	-4.9	-29.1	81.2	-23.7	0	-8.1
142	GTGTTGAGGGCAGTCCACCG SEQ ID NO:1219	-4.9	-29.3	80.9	-23.3	-1	-5.6
146	CACAGTGTTGAGGGCAGTCC SEQ ID NO:1220	-4.9	-27.2	79.2	-22.3	0	-5.8
370	GAAGGTGCCGTAGGGACAGT SEQ ID NO:1221	-4.9	-26.9	75.5	-20.4	-1.5	-6.7
454	GAAGAAGGGGAATTTCAGGC SEQ ID NO:1222	-4.9	-21.6	63.7	-16	-0.5	-5
647	CAATCACGAAAATAGAGCCT SEQ ID NO:1223	-4.9	-19.6	57.2	-14.7	0	-3.5
805	CAAACACATACAAGTGTTCA SEQ ID NO:1224	-4.9	-18.6	57	-10.9	-2.8	-8.2
959	AAAGAACTAATTTGACTCAC SEQ ID NO:1225	-4.9	-15.8	51.2	-10.9	0	-2.7
1631	CACAGCACTTATGTTTAAAT SEQ ID NO:1226	-4.9	-18.7	57.6	-13.8	0	-5.4
1798	TAAGAACATCTAGTACAACA SEQ ID NO:1227	-4.9	-16.8	53.6	-11.9	0	-5.7
1920	AAAGGCCTTCCACACACATT SEQ ID NO:1228	-4.9	-24.5	68.2	-18.1	-1	-10.6
1928	TTACATTCAAAGGCCTTCCA SEQ ID NO:1229	-4.9	-23.6	67.3	-17.2	-1	-10.6
1933	CAGCTTTACATTCAAAGGCC SEQ ID NO:1230	-4.9	-23	66.5	-17.3	-0.6	-6.4
55	CTTCATGTTTCCCAGCTGCC SEQ ID NO:1231	-4.8	-29.1	81.2	-23.8	0	-8.1
166	GCTTTTGCACTCACTGCTGT SEQ ID NO:1232	-4.8	-26.7	77.7	-20	-1.9	-7.4
181	CTTGCAGCGCGGGCTGCTTT SEQ ID NO:1233	-4.8	-30.7	81.8	-19.7	-6.2	-16.3
253	TGTGCGGTAGCAAGTTTCTC SEQ ID NO:1234	-4.8	-24.8	73.3	-18	-2	-5.6
464	CTGAATATTGGAAGAAGGGG SEQ ID NO:1235	-4.8	-19.2	57.9	-14.4	0	-4.6
522	TCTCCAGATGCCATGTCATG SEQ ID NO:1236	-4.8	-25.8	73.9	-20.5	-0.1	-4.3
802	ACACATACAAGTGTTCAGTC SEQ ID NO:1237	-4.8	-20.9	64.6	-14.7	-1.3	-5.4
814	AATATTTAACAAACACATAC SEQ ID NO:1238	-4.8	-13.4	46.1	-8.6	0	-3.8
960	CAAAGAACTAATTTGACTCA SEQ ID NO:1239	-4.8	-16.3	52	-10.9	-0.3	-3.6
1003	TTAAGTCTTCATTCCATATC SEQ ID NO:1240	-4.8	-20.1	62.7	-15.3	0	-2.7
1231	ATCAGCAGCCTTTTGAAATT SEQ ID NO:1241	-4.8	-21.9	64.4	-17.1	0	-4.5
1316	GGCATACGTTAAAGCTATTT SEQ ID NO:1242	-4.8	-20.6	61.2	-15.1	-0.4	-5.1
1319	GGTGGCATACGTTAAAGCTA SEQ ID NO:1243	-4.8	-22.8	66	-17.3	-0.4	-5.4
1720	TTGACATGTTTTCTGCTGAA SEQ ID NO:1244	-4.8	-21	63.6	-14.6	-0.1	-11.4
1727	TTTAAAGTTGACATGTTTTC SEQ ID NO:1245	-4.8	-17.2	55.6	-12.4	0	-7.1
1803	TTTCCTAAGAACATCTAGTA SEQ ID NO:1246	-4.8	-19.2	59.6	-13.9	-0.2	-4.2

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1888	GGCCAACTTCAAGAATAAAA SEQ ID NO:1247	-4.8	-18.1	54.5	-13.3	0	-7
96	AGGTGTGCAGGCACGAGGAG SEQ ID NO:1248	-4.7	-27.2	77.1	-20	-2.5	-10.7
309	TTAGAAGGCTGACACCTCAG SEQ ID NO:1249	-4.7	-23.3	67.9	-17	-1.6	-5.1
832	CAAATCTACATGCATTCGAA SEQ ID NO:1250	-4.7	-18.9	56.6	-14.2	0	-6.8
953	CTAATTTGACTCACTGCGGT SEQ ID NO:1251	-4.7	-23	66.6	-18.3	0	-6
982	CAACATTAATGTACATCAAA SEQ ID NO:1252	-4.7	-15.5	50.2	-9.5	-0.2	-10.5
1079	CTAGAGAAGCTACCTACCAA SEQ ID NO:1253	-4.7	-22.5	64.8	-17.8	0	-5.1
1380	ATTTACCTTCATACACACAC SEQ ID NO:1254	-4.7	-20.8	62.4	-16.1	0	-0.9
1462	GATTTCTTTCCTCAAGAGGA SEQ ID NO:1255	-4.7	-22.4	67.3	-16.2	-1.3	-9.9
1487	TAACCATTTTCAACAAATAA SEQ ID NO:1256	-4.7	-15.1	49	-10.4	0.1	-2.7
1573	ATCCAGAGTGACTCCTATAA SEQ ID NO:1257	-4.7	-22.6	66.7	-17.9	0.4	-4.7
1743	CTAATTCCACCTATATTTTA SEQ ID NO:1258	-4.7	-19.6	59.4	-14.9	0	-2.9
1970	AAACATGTCCTTTTAAAACA SEQ ID NO:1259	-4.7	-16.8	52.6	-12.1	0	-6.9
285	GGGCCACACTTCATGCCATC SEQ ID NO:1260	-4.6	-29	79.7	-22.2	-2.2	-7.6
376	CATCCCGAAGGTGCCGTAGG SEQ ID NO:1261	-4.6	-28.9	75.8	-22	-2.3	-6.7
496	GAGAGAAACAAATCTGTTGG SEQ ID NO:1262	-4.6	-17.7	55.1	-11.5	-1.5	-4.5
1250	CAGGTAACCCGGGAACTACA SEQ ID NO:1263	-4.6	-25.1	68.1	-18.9	-1.1	-11
1368	ACACACACAAACCACCAGTG SEQ ID NO:1264	-4.6	-23.2	64.7	-18	-0.3	-5.2
1437	AATATGGGTAGGGAAGATGA SEQ ID NO:1265	-4.6	-19.8	60	-15.2	0	-2.7
1550	TGGATAATAAATTTATCATG SEQ ID NO:1266	-4.6	-14.1	47.8	-6.9	-2.6	-8.1
1551	ATGGATAATAAATTTATCAT SEQ ID NO:1267	-4.6	-14.1	47.8	-6.9	-2.6	-8.1
1565	TGACTCCTATAATTATGGAT SEQ ID NO:1268	-4.6	-19.3	59	-14	-0.1	-9
1719	TGACATGTTTTCTGCTGAAA SEQ ID NO:1269	-4.6	-20.2	61.1	-14.1	-1.1	-10.4
1930	CTTTACATTCAAAGGCCTTC SEQ ID NO:1270	-4.6	-21.9	64.7	-16	0	-10.6
1964	GTCCTTTTAAAACAAAACCT SEQ ID NO:1271	-4.6	-18.3	55	-13.1	-0.3	-6.2
975	AATGTACATCAAAGTCAAAG SEQ ID NO:1272	-4.5	-15.7	51	-10.6	0	-8.4
1248	GGTAACCCGGGAACTACATC SEQ ID NO:1273	-4.5	-24.8	68.2	-18.8	-0.2	-11
1338	TTCTTAGATTTATCTCTGAG SEQ ID NO:1274	-4.5	-18.9	60.9	-13.7	-0.4	-5.6
1523	TGTTTGAAAACCTTATAGAG SEQ ID NO:1275	-4.5	-17.1	54	-12.1	-0.1	-5.7
1620	TGTTTAAATAAGGTCCCTCT SEQ ID NO:1276	-4.5	-21.7	64.2	-17.2	0	-5.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1668	CTTATTTTCATACCTTAAAT SEQ ID NO:1277	-4.5	-17.3	54.7	-12.8	0	-2.7
262	GCCTGAGACTGTGCGGTAGC SEQ ID NO:1278	-4.4	-28.7	80.3	-23.6	-0.5	-5.4
823	ATGCATTCGAATATTTAACA SEQ ID NO:1279	-4.4	-17.5	54.2	-12.5	0	-8.4
1247	GTAACCCGGGAACTACATCA SEQ ID NO:1280	-4.4	-24.3	67	-18.5	-0.2	-10.7
1464	TAGATTTCTTTCCTCAAGAG SEQ ID NO:1281	-4.4	-20.3	62.9	-14.9	-0.9	-6.8
1522	GTTTGAAAACCTTATAGAGT SEQ ID NO:1282	-4.4	-18.3	56.9	-13.9	0	-4.7
1566	GTGACTCCTATAATTATGGA SEQ ID NO:1283	-4.4	-20.5	62	-15.5	0	-8.5
1618	TTTAAATAAGGTCCCTCTGT SEQ ID NO:1284	-4.4	-21.7	64.2	-17.3	0	-4.7
1658	TACCTTAAATTGAAAATTCA SEQ ID NO:1285	-4.4	-15	49	-9.3	-1.2	-5.5
1684	ACAAACCTCCTAAAAACTTA SEQ ID NO:1286	-4.4	-17.7	53.6	-13.3	0	-1.2
1685	TACAAACCTCCTAAAAACTT SEQ ID NO:1287	-4.4	-17.7	53.6	-13.3	0	-0.9
1724	AAAGTTGACATGTTTTCTGC SEQ ID NO:1288	-4.4	-20	61.6	-15.6	0	-7.1
1969	AACATGTCCTTTTAAAACAA SEQ ID NO:1289	-4.4	-16.8	52.6	-12.4	0	-6.9
95	GGTGTGCAGGCACGAGGAGC SEQ ID NO:1290	-4.3	-29	81.3	-22.2	-2.5	-10.7
255	ACTGTGCGGTAGCAAGTTTC SEQ ID NO:1291	-4.3	-24.6	72.2	-18	-2.3	-6.4
274	CATGCCATCCATGCCTGAGA SEQ ID NO:1292	-4.3	-28.2	76.3	-22.6	-1.2	-5.7
343	GATACCAAACTCTTCACCAA SEQ ID NO:1293	-4.3	-21.6	62.2	-17.3	0	-1.9
387	TCTCTGCAATCCATCCCGAA SEQ ID NO:1294	-4.3	-26.6	71.9	-22.3	0	-4.9
426	GTCCCCCTGTCACAGATGCC SEQ ID NO:1295	-4.3	-32.1	86	-27.2	-0.3	-5.2
455	GGAAGAAGGGGAATTTCAGG SEQ ID NO:1296	-4.3	-21	62.2	-16	-0.5	-5
826	TACATGCATTCGAATATTTA SEQ ID NO:1297	-4.3	-17.9	55.5	-13	0	-8.4
1331	ATTTATCTCTGAGGTGGCAT SEQ ID NO:1298	-4.3	-23.2	70	-18.9	0	-6.2
1552	TATGGATAATAAATTTATCA SEQ ID NO:1299	-4.3	-13.8	47.3	-6.9	-2.6	-8.1
1660	CATACCTTAAATTGAAAATT SEQ ID NO:1300	-4.3	-14.6	48	-9.2	-1	-3.5
1671	AAACTTATTTTCATACCTTA SEQ ID NO:1301	-4.3	-17.5	55.2	-13.2	0	-1.9
1745	TCCTAATTCCACCTATATTT SEQ ID NO:1302	-4.3	-22.2	64.7	-17.9	0	-2.9
1801	TCCTAAGAACATCTAGTACA SEQ ID NO:1303	-4.3	-19.9	60.7	-15.6	0	-5.7
1897	AACTCTGTTGGCCAACTTCA SEQ ID NO:1304	-4.3	-24.3	69.8	-16.6	-0.5	-15
431	TTCCCGTCCCCCTGTCACAG SEQ ID NO:1305	-4.2	-33	85.5	-28.8	0	-4.6
615	CACAGCCGGGATCAGCGTGG SEQ ID NO:1306	-4.2	-29.3	77.8	-23.6	-1.4	-7.7

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
804	AAACACATACAAGTGTTCAG SEQ ID NO:1307	-4.2	-17.9	55.9	-10.9	-2.8	-8.2
821	GCATTCGAATATTTAACAAA SEQ ID NO:1308	-4.2	-16.1	51	-11.2	0	-8.7
976	TAATGTACATCAAAGTCAAA SEQ ID NO:1309	-4.2	-15.4	50.3	-10.6	0	-8.4
1051	TAAATATTTTATTTCCCACT SEQ ID NO:1310	-4.2	-18.4	56.6	-13.4	-0.6	-6.2
1199	AAGCTGTTTGTTACTCAAAT SEQ ID NO:1311	-4.2	-19.2	59.3	-13.4	-1.6	-9.4
1807	GATATTTCCTAAGAACATCT SEQ ID NO:1312	-4.2	-18.9	58.3	-14	-0.5	-4
1858	TACTGAAATAATTCTTAAAT SEQ ID NO:1313	-4.2	-12.8	45.1	-7.4	-1.1	-4.2
185	TCCTCTTGCAGCGCGGGCTG SEQ ID NO:1314	-4.1	-31.5	83.7	-24.2	-3.2	-10.9
567	CCGGCAGCATTCTCTTTCAC SEQ ID NO:1315	-4.1	-27.2	76.6	-23.1	0	-5.3
593	TTAACCATTTCCTCATTACG SEQ ID NO:1316	-4.1	-21.4	62.2	-17.3	0	-3
854	GTTACTATACACACACATTT SEQ ID NO:1317	-4.1	-19.3	59.7	-15.2	0	-2
1377	TACCTTCATACACACACAAA SEQ ID NO:1318	-4.1	-19.9	59	-15.8	0	-0.9
1389	TATATAAATATTTACCTTCA SEQ ID NO:1319	-4.1	-15.6	51.1	-11	0	-7.9
1578	TTGAAATCCAGAGTGACTCC SEQ ID NO:1320	-4.1	-22.3	65.2	-17.5	-0.4	-5.5
1833	CTTCACTTCAAATAAAATAC SEQ ID NO:1321	-4.1	-14.5	48.4	-10.4	0	-1.2
180	TTGCAGCGCGGGCTGCTTTT SEQ ID NO:1322	-4	-29.9	80.4	-19.7	-6.2	-16.3
312	CCATTAGAAGGCTGACACCT SEQ ID NO:1323	-4	-24.9	69.7	-20.2	-0.4	-4
457	TTGGAAGAAGGGGAATTTCA SEQ ID NO:1324	-4	-19.9	59.8	-15.2	-0.5	-5
621	AGAAATCACAGCCGGGATCA SEQ ID NO:1325	-4	-23.9	66.8	-19.9	0	-6.9
803	AACACATACAAGTGTTCAGT SEQ ID NO:1326	-4	-19.8	60.9	-13.5	-2.3	-7.4
1137	GGTTGTTTTATTTTGACTTT SEQ ID NO:1327	-4	-19.9	62.7	-15.9	0	-2.8
1510	TATAGAGTCATAGGTTTTTA SEQ ID NO:1328	-4	-18.5	60	-14.5	0	-4.8
1572	TCCAGAGTGACTCCTATAAT SEQ ID NO:1329	-4	-22.6	66.7	-17.9	-0.4	-5.5
1759	TCTTTCAAATATACTCCTAA SEQ ID NO:1330	-4	-18	56.3	-14	0	-2.7
1851	ATAATTCTTAAATAAGTTCT SEQ ID NO:1331	-4	-14.4	49	-10.4	0	-4.9
68	GCAGCAAGACGCTCTTCATG SEQ ID NO:1332	-3.9	-25.1	71.3	-19.9	-1.2	-6.4
74	TGGTCAGCAGCAAGACGCTC SEQ ID NO:1333	-3.9	-26.5	75.3	-21.1	-1.4	-8.5
341	TACCAAACTCTTCACCAAAA SEQ ID NO:1334	-3.9	-19.6	57.4	-15.7	0	-1
520	TCCAGATGCCATGTCATGCT SEQ ID NO:1335	-3.9	-27.2	76.6	-22.8	-0.2	-4.6
670	TAAAATGTTGGCTGTGTGTT SEQ ID NO:1336	-3.9	-20.5	62.2	-16.6	0	-3.9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1054	GGCTAAATATTTTATTTCCC SEQ ID NO:1337	-3.9	-20.5	61.2	-15.8	-0.6	-8.2
1334	TAGATTTATCTCTGAGGTGG SEQ ID NO:1338	-3.9	-21	65.4	-16.2	-0.7	-6.2
1390	ATATATAAATATTTACCTTC SEQ ID NO:1339	-3.9	-14.9	49.8	-11	0	-7.4
1687	TTTACAAACCTCCTAAAAAC SEQ ID NO:1340	-3.9	-16.9	52.2	-13	0	-2.2
141	TGTTGAGGGCAGTCCACCGC SEQ ID NO:1341	-3.8	-29.9	81.8	-25	-1	-5.6
143	AGTGTTGAGGGCAGTCCACC SEQ ID NO:1342	-3.8	-28.5	81.8	-23.6	-1	-5.6
278	ACTTCATGCCATCCATGCCT SEQ ID NO:1343	-3.8	-28.6	78.1	-23	-1.8	-5
373	CCCGAAGGTGCCGTAGGGAC SEQ ID NO:1344	-3.8	-29.8	77.4	-23.3	-2.7	-7.9
618	AATCACAGCCGGGATCAGCG SEQ ID NO:1345	-3.8	-26.6	71.7	-21.9	-0.7	-6.9
822	TGCATTCGAATATTTAACAA SEQ ID NO:1346	-3.8	-16.8	52.6	-12.4	0	-8.4
967	TCAAAGTCAAAGAACTAATT SEQ ID NO:1347	-3.8	-14.7	48.8	-10.9	0	-3
1180	TTTCCATAAGCTTCAAACAT SEQ ID NO:1348	-3.8	-19.7	59.2	-15.9	0	-6.8
1760	TTCTTTCAAATATACTCCTA SEQ ID NO:1349	-3.8	-18.8	58.5	-15	0	-2.7
1811	CTGAGATATTTCCTAAGAAC SEQ ID NO:1350	-3.8	-18.4	57.1	-14.1	-0.2	-4.6
1859	ATACTGAAATAATTCTTAAA SEQ ID NO:1351	-3.8	-12.8	45.1	-8.3	-0.4	-3.5
1891	GTTGGCCAACTTCAAGAATA SEQ ID NO:1352	-3.8	-21.5	62.9	-14.7	0	-14.2
82	GAGGAGCGTGGTCAGCAGCA SEQ ID NO:1353	-3.7	-28.7	81.5	-24.1	-0.7	-5.9
1119	TTTCCCAAAGCCAAAAAAAA SEQ ID NO:1354	-3.7	-17.5	51.9	-13.8	0	-3.2
1189	TTACTCAAATTTCCATAAGC SEQ ID NO:1355	-3.7	-18.7	57.4	-15	0	-4.5
1314	CATACGTTAAAGCTATTTAT SEQ ID NO:1356	-3.7	-17.3	54.3	-13	-0.3	-5.7
1482	ATTTTCAACAAATAATACTA SEQ ID NO:1357	-3.7	-13.7	46.9	-10	0	-2.5
1571	CCAGAGTGACTCCTATAATT SEQ ID NO:1358	-3.7	-22.3	65.5	-17.9	-0.4	-5.5
1802	TTCCTAAGAACATCTAGTAC SEQ ID NO:1359	-3.7	-19.3	59.8	-15.6	0	-4
1927	TACATTCAAAGGCCTTCCAC SEQ ID NO:1360	-3.7	-23.7	67.5	-18.5	-1	-10.6
277	CTTCATGCCATCCATGCCTG SEQ ID NO:1361	-3.6	-28.4	77.3	-23	-1.8	-5
404	ACTGGCAGTTGCAGGTCTCT SEQ ID NO:1362	-3.6	-27.6	81.7	-23	-0.9	-6.6
961	TCAAAGAACTAATTTGACTC SEQ ID NO:1363	-3.6	-16	51.9	-10.9	-1.4	-5.4
1057	AAGGGCTAAATATTTTATTT SEQ ID NO:1364	-3.6	-16.6	53.2	-12.3	-0.4	-8.2
1472	AATAATACTAGATTTCTTTC SEQ ID NO:1365	-3.6	-15.5	51.8	-11.9	0	-4.5
1559	CTATAATTATGGATAATAAA SEQ ID NO:1366	-3.6	-12.5	44.5	-8.3	-0.3	-5.9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1577	TGAAATCCAGAGTGACTCCT SEQ ID NO:1367	-3.6	-23.1	66.8	-18.8	-0.4	-5.5
1728	TTTTAAAGTTGACATGTTTT SEQ ID NO:1368	-3.6	-16.9	54.6	-13.3	0	-7.1
1763	AGATTCTTTCAAATATACTC SEQ ID NO:1369	-3.6	-16.8	54.7	-12.7	-0.1	-3.3
1832	TTCACTTCAAATAAAATACT SEQ ID NO:1370	-3.6	-14.5	48.4	-10.9	0	-1.2
1926	ACATTCAAAGGCCTTCCACA SEQ ID NO:1371	-3.6	-24.7	69.1	-19.6	-1	-10.6
1959	TTTAAAACAAAACCTAACAG SEQ ID NO:1372	-3.6	-13.6	45.9	-10	0	-4
105	GCGGCCACCAGGTGTGCAGG SEQ ID NO:1373	-3.5	-32.5	86.1	-26.4	-2.5	-12.5
286	CGGGCCACACTTCATGCCAT SEQ ID NO:1374	-3.5	-29.4	77.6	-23.7	-2.2	-7.6
291	AGCCCCGGGCCACACTTCAT SEQ ID NO:1375	-3.5	-32.7	83.6	-27.3	-1.8	-11.2
346	GCAGATACCAAACTCTTCAC SEQ ID NO:1376	-3.5	-22.1	64.8	-18.6	0	-3.4
966	CAAAGTCAAAGAACTAATTT SEQ ID NO:1377	-3.5	-14.4	48.1	-10.9	0	-3
1918	AGGCCTTCCACACACATTCA SEQ ID NO:1378	-3.5	-27	75.4	-22.4	-1	-7.9
207	CAGCCACAGTCGTCGAGCAC SEQ ID NO:1379	-3.4	-28.2	77.5	-24.2	-0.3	-4.9
252	GTGCGGTAGCAAGTTTCTCC SEQ ID NO:1380	-3.4	-26.8	77.3	-21.4	-2	-5.5
356	GACAGTCTTTGCAGATACCA SEQ ID NO:1381	-3.4	-23.9	70.3	-20.5	0.3	-5.2
1082	ATTCTAGAGAAGCTACCTAC SEQ ID NO:1382	-3.4	-21	63.8	-17.6	0	-5.8
1182	AATTTCCATAAGCTTCAAAC SEQ ID NO:1383	-3.4	-18.3	56.1	-14.9	0	-6.8
1486	AACCATTTTCAACAAATAAT SEQ ID NO:1384	-3.4	-15.4	49.5	-11.5	-0.1	-2.7
1555	AATTATGGATAATAAATTTA SEQ ID NO:1385	-3.4	-12.1	43.7	-8.1	-0.3	-6.1
12	GTCTTTGCTGGTGGGAAGCA SEQ ID NO:1386	-3.3	-26.6	77.2	-21.8	-1.4	-5.7
175	GCGCGGGCTGCTTTTGCACT SEQ ID NO:1387	-3.3	-30.9	82.1	-25.1	-2.5	-11.8
290	GCCCCGGGCCACACTTCATG SEQ ID NO:1388	-3.3	-32.7	83.1	-28.1	-1	-10
308	TAGAAGGCTGACACCTCAGC SEQ ID NO:1389	-3.3	-25	71.8	-17.8	-3.9	-9.4
383	TGCAATCCATCCCGAAGGTG SEQ ID NO:1390	-3.3	-26.4	70.9	-21.8	-1.2	-6.9
649	AACAATCACGAAAATAGAGC SEQ ID NO:1391	-3.3	-16.2	50.9	-12.9	0	-3.5
833	ACAAATCTACATGCATTCGA SEQ ID NO:1392	-3.3	-19.8	58.9	-16.5	0	-6.7
1160	CTTACTTCCTTCAGGGGTTT SEQ ID NO:1393	-3.3	-25.4	75	-21.6	-0.2	-4.7
1183	AAATTTCCATAAGCTTCAAA SEQ ID NO:1394	-3.3	-17.4	53.9	-14.1	0	-6.8
1438	AAATATGGGTAGGGAAGATG SEQ ID NO:1395	-3.3	-18.5	56.8	-15.2	0	-2.7
1473	AAATAATACTAGATTTCTTT SEQ ID NO:1396	-3.3	-14.4	48.9	-11.1	0	-4.5

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1558	TATAATTATGGATAATAAAT SEQ ID NO:1397	-3.3	-11.6	42.7	-8.3	0.2	-5.9
1625	ACTTATGTTTAAATAAGGTC SEQ ID NO:1398	-3.3	-16.4	53.5	-11.5	-1.5	-7.1
1995	TTGTTCTTTTTTATTGAACA SEQ ID NO:1399	-3.3	-17.8	57	-12.4	-2.1	-6.7
174	CGCGGGCTGCTTTTGCACTC SEQ ID NO:1400	-3.2	-29.5	79.6	-24.2	-2.1	-11.3
623	TCAGAAATCACAGCCGGGAT SEQ ID NO:1401	-3.2	-23.9	66.8	-20.7	0	-6.9
897	TCTCCATGTAAGATTACCTA SEQ ID NO:1402	-3.2	-21.8	64.9	-18.6	0	-4.9
1152	CTTCAGGGGTTTTCTGGTTG SEQ ID NO:1403	-3.2	-25	75.1	-20.9	-0.7	-4.2
1232	CATCAGCAGCCTTTTGAAAT SEQ ID NO:1404	-3.2	-22.5	65.2	-19.3	0	-4.1
1372	TCATACACACACAAACCACC SEQ ID NO:1405	-3.2	-22.1	62.6	-18.9	0	-0.9
1403	TTTATTTATAAAAATATATA SEQ ID NO:1406	-3.2	-9.8	39.4	-5.3	-1.2	-6.5
1560	CCTATAATTATGGATAATAA SEQ ID NO:1407	-3.2	-15.2	49.6	-11.5	-0.1	-6.5
463	TGAATATTGGAAGAAGGGGA SEQ ID NO:1408	-3.1	-18.9	57.3	-15.8	0	-4.6
856	GTGTTACTATACACACACAT SEQ ID NO:1409	-3.1	-20.3	62	-15.6	-1.5	-6.3
948	TTGACTCACTGCGGTCTTCA SEQ ID NO:1410	-3.1	-25.5	73.9	-21.4	-0.9	-6.2
1766	CTAAGATTCTTTCAAATATA SEQ ID NO:1411	-3.1	-15.2	50.6	-11.6	-0.1	-5.6
1796	AGAACATCTAGTACAACAGT SEQ ID NO:1412	-3.1	-19	59.2	-15.9	0	-5.7
56	TCTTCATGTTTCCCAGCTGC SEQ ID NO:1413	-3	-27.5	79.4	-24	0	-8.1
83	CGAGGAGCGTGGTCAGCAGC SEQ ID NO:1414	-3	-28.8	80	-24.8	-0.9	-5.9
225	GCAGCGCACACTCGGCAGCA SEQ ID NO:1415	-3	-31	82.1	-25.7	-2.3	-8.5
371	CGAAGGTGCCGTAGGGACAG SEQ ID NO:1416	-3	-26.5	72.1	-21.9	-1.5	-6.7
448	GGGGAATTTCAGGCATTTTC SEQ ID NO:1417	-3	-23.2	68.8	-20.2	0	-5
509	TGTCATGCTCCGTGAGAGAA SEQ ID NO:1418	-3	-24.5	70.3	-20.4	-1	-6.1
896	CTCCATGTAAGATTACCTAA SEQ ID NO:1419	-3	-20.7	61.4	-17.7	0	-4.9
1140	TCTGGTTGTTTTATTTTGAC SEQ ID NO:1420	-3	-20.1	63.4	-17.1	0	-2
1320	AGGTGGCATACGTTAAAGCT SEQ ID NO:1421	-3	-23.1	66.7	-19.5	-0.3	-5.1
1376	ACCTTCATACACACACAAAC SEQ ID NO:1422	-3	-20.4	60	-17.4	0	-0.9
1388	ATATAAATATTTACCTTCAT SEQ ID NO:1423	-3	-15.9	51.7	-12.4	0	-7.9
1831	TCACTTCAAATAAAATACTT SEQ ID NO:1424	-3	-14.5	48.4	-11.5	0	-1.2
1857	ACTGAAATAATTCTTAAATA SEQ ID NO:1425	-3	-12.8	45.1	-8.6	-1.1	-4.2
1925	CATTCAAAGGCCTTCCACAC SEQ ID NO:1426	-3	-24.7	69.1	-20.2	-1	-10.6

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1957	TAAAACAAAACCTAACAGCT SEQ ID NO:1427	-3	-16.1	50.3	-13.1	0	-4.3
1958	TTAAAACAAAACCTAACAGC SEQ ID NO:1428	-3	-15.3	49	-12.3	0	-2.8
594	TTTAACCATTTCCTCATTAC SEQ ID NO:1429	-2.9	-20.7	62.1	-17.8	0	-2.4
957	AGAACTAATTTGACTCACTG SEQ ID NO:1430	-2.9	-18.1	56.6	-15.2	0	-2.7
1461	ATTTCTTTCCTCAAGAGGAT SEQ ID NO:1431	-2.9	-21.8	65.9	-17.3	-1.5	-10.2
1567	AGTGACTCCTATAATTATGG SEQ ID NO:1432	-2.9	-19.9	60.9	-17	0	-6.9
1579	TTTGAAATCCAGAGTGACTC SEQ ID NO:1433	-2.9	-20.4	61.9	-17.5	0	-5.1
1691	TTCTTTTACAAACCTCCTAA SEQ ID NO:1434	-2.9	-20.3	60.4	-17.4	0	-1.9
1808	AGATATTTCCTAAGAACATC SEQ ID NO:1435	-2.9	-18	56.5	-14.4	-0.5	-4
1968	ACATGTCCTTTTAAAACAAA SEQ ID NO:1436	-2.9	-16.8	52.6	-13.9	0	-6.2
57	CTCTTCATGTTTCCCAGCTG SEQ ID NO:1437	-2.8	-26.6	76.9	-23.3	0	-7.8
94	GTGTGCAGGCACGAGGAGCG SEQ ID NO:1438	-2.8	-28.6	78.3	-24	-1.7	-10.7
102	GCCACCAGGTGTGCAGGCAC SEQ ID NO:1439	-2.8	-31.4	85.9	-25.8	-2.1	-13.5
218	ACACTCGGCAGCAGCCACAG SEQ ID NO:1440	-2.8	-28.8	78.4	-22.8	-3.2	-9.8
222	GCGCACACTCGGCAGCAGCC SEQ ID NO:1441	-2.8	-32.3	84.4	-27.2	-2.1	-12
305	AAGGCTGACACCTCAGCCCC SEQ ID NO:1442	-2.8	-30.7	81.2	-21.8	-6.1	-13.4
372	CCGAAGGTGCCGTAGGGACA SEQ ID NO:1443	-2.8	-28.5	75.1	-23.5	-2.2	-8.6
624	CTCAGAAATCACAGCCGGGA SEQ ID NO:1444	-2.8	-24.8	68.6	-22	0	-6.9
898	GTCTCCATGTAAGATTACCT SEQ ID NO:1445	-2.8	-23.3	68.7	-20.5	0	-5.5
965	AAAGTCAAAGAACTAATTTG SEQ ID NO:1446	-2.8	-13.7	46.8	-10.9	0.1	-3.8
1091	CACAATTAAATTCTAGAGAA SEQ ID NO:1447	-2.8	-14.9	49.3	-12.1	0	-5.8
1239	GGAACTACATCAGCAGCCTT SEQ ID NO:1448	-2.8	-25.2	71.8	-22.4	0	-4.5
1381	TATTTACCTTCATACACACA SEQ ID NO:1449	-2.8	-20.3	61.3	-17.5	0	-1.1
1994	TGTTCTTTTTTATTGAACAA SEQ ID NO:1450	-2.8	-17	54.8	-12.1	-2.1	-6.6
81	AGGAGCGTGGTCAGCAGCAA SEQ ID NO:1451	-2.7	-27.4	77.4	-23.1	-1.5	-5.9
84	ACGAGGAGCGTGGTCAGCAG SEQ ID NO:1452	-2.7	-27.2	76.2	-23.3	-1.1	-6.3
296	ACCTCAGCCCCGGGCCACAC SEQ ID NO:1453	-2.7	-34.8	87	-30.2	-1.8	-11.2
697	GTACTTATGCTATATCTAGA SEQ ID NO:1454	-2.7	-19.5	61.6	-16.8	0	-5.8
1561	TCCTATAATTATGGATAATA SEQ ID NO:1455	-2.7	-16.3	52.4	-12.9	0	-8.7
1619	GTTTAAATAAGGTCCCTCTG SEQ ID NO:1456	-2.7	-21.7	64.2	-19	0	-4.8

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1679	CCTCCTAAAAACTTATTTTC SEQ ID NO:1457	-2.7	-18.7	56.8	-15	-0.9	-3.3
1815	ACTTCTGAGATATTTCCTAA SEQ ID NO:1458	-2.7	-19.9	61.2	-17.2	0	-3.8
98	CCAGGTGTGCAGGCACGAGG SEQ ID NO:1459	-2.6	-29.3	80.1	-24.2	-2.5	-10.7
172	CGGGCTGCTTTTGCACTCAC SEQ ID NO:1460	-2.6	-27.8	77.3	-23.2	-2	-8.4
338	CAAACTCTTCACCAAAAGGA SEQ ID NO:1461	-2.6	-19.5	57.6	-16.9	0	-3.7
671	CTAAAATGTTGGCTGTGTGT SEQ ID NO:1462	-2.6	-21.3	63.8	-18.7	0	-3.9
700	CATGTACTTATGCTATATCT SEQ ID NO:1463	-2.6	-19.9	61.8	-17.3	0	-4.8
946	GACTCACTGCGGTCTTCAGC SEQ ID NO:1464	-2.6	-27.2	78.5	-23.9	-0.4	-6
1581	TTTTTGAAATCCAGAGTGAC SEQ ID NO:1465	-2.6	-19.3	59.2	-16.7	0	-3
1659	ATACCTTAAATTGAAAATTC SEQ ID NO:1466	-2.6	-14.3	47.8	-10.4	-1.2	-3.7
1680	ACCTCCTAAAAACTTATTTT SEQ ID NO:1467	-2.6	-18.5	56.1	-15	-0.7	-3.2
1686	TTACAAACCTCCTAAAAACT SEQ ID NO:1468	-2.6	-17.7	53.6	-15.1	0	-1.2
1805	TATTTCCTAAGAACATCTAG SEQ ID NO:1469	-2.6	-18	56.6	-14.9	-0.2	-3.6
1854	GAAATAATTCTTAAATAAGT SEQ ID NO:1470	-2.6	-12.2	44	-8.9	-0.4	-4.9
1952	CAAAACCTAACAGCTTATGC SEQ ID NO:1471	-2.6	-19.9	58.5	-16.6	-0.5	-4.5
64	CAAGACGCTCTTCATGTTTC SEQ ID NO:1472	-2.5	-22.6	67	-19.3	-0.6	-6.1
276	TTCATGCCATCCATGCCTGA SEQ ID NO:1473	-2.5	-28.1	76.7	-23.8	-1.8	-5
406	TGACTGGCAGTTGCAGGTCT SEQ ID NO:1474	-2.5	-26.9	78.8	-24.4	1.7	-6.1
510	ATGTCATGCTCCGTGAGAGA SEQ ID NO:1475	-2.5	-25.2	72.7	-21.6	-1	-6.1
592	TAACCATTTCCTCATTACGG SEQ ID NO:1476	-2.5	-22.5	64.3	-20	0	-3.5
699	ATGTACTTATGCTATATCTA SEQ ID NO:1477	-2.5	-18.9	59.9	-16.4	0	-4.8
1200	AAAGCTGTTTGTTACTCAAA SEQ ID NO:1478	-2.5	-18.5	57.4	-14.5	-1.4	-7.8
1471	ATAATACTAGATTTCTTTCC SEQ ID NO:1479	-2.5	-18.2	57.8	-15.7	0	-4.5
1931	GCTTTACATTCAAAGGCCTT SEQ ID NO:1480	-2.5	-23.3	67.4	-19.5	-0.6	-10.4
173	GCGGGCTGCTTTTGCACTCA SEQ ID NO:1481	-2.4	-29.4	81.1	-24.9	-2.1	-8.4
279	CACTTCATGCCATCCATGCC SEQ ID NO:1482	-2.4	-28.4	77.2	-24.7	-1.2	-4.4
382	GCAATCCATCCCGAAGGTGC SEQ ID NO:1483	-2.4	-28.2	74.9	-24.5	-1.2	-5.6
456	TGGAAGAAGGGGAATTTCAG SEQ ID NO:1484	-2.4	-19.8	59.6	-16.8	-0.3	-5
824	CATGCATTCGAATATTTAAC SEQ ID NO:1485	-2.4	-17.5	54.2	-14.6	0	-8.2
857	AGTGTTACTATACACACACA SEQ ID NO:1486	-2.4	-20.3	62.3	-15.6	-2.3	-7.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
964	AAGTCAAAGAACTAATTTGA SEQ ID NO:1487	-2.4	-15	49.6	-10.9	-1.7	-6
1052	CTAAATATTTTATTTCCCAC SEQ ID NO:1488	-2.4	-18.4	56.6	-15.2	-0.6	-6.2
1402	TTATTTATAAAAATATATAA SEQ ID NO:1489	-2.4	-9	37.9	-5.3	-1.2	-6.5
1439	TAAATATGGGTAGGGAAGAT SEQ ID NO:1490	-2.4	-18.2	56.3	-15.8	0	-2.7
1444	GATGATAAATATGGGTAGGG SEQ ID NO:1491	-2.4	-18.9	57.9	-16.5	0	-2.7
1887	GCCAACTTCAAGAATAAAAT SEQ ID NO:1492	-2.4	-16.9	52.2	-14.5	0	-3.5
53	TCATGTTTCCCAGCTGCCTC SEQ ID NO:1493	-2.3	-29.4	82.6	-26.6	0	-8.1
99	ACCAGGTGTGCAGGCACGAG SEQ ID NO:1494	-2.3	-28.3	78.1	-24.2	-1.7	-10.7
100	CACCAGGTGTGCAGGCACGA SEQ ID NO:1495	-2.3	-29	78.8	-24.2	-2.5	-10.7
340	ACCAAACTCTTCACCAAAAG SEQ ID NO:1496	-2.3	-19.9	58	-17.6	0	-2.6
386	CTCTGCAATCCATCCCGAAG SEQ ID NO:1497	-2.3	-26.2	70.7	-23.9	0	-4.9
508	GTCATGCTCCGTGAGAGAAA SEQ ID NO:1498	-2.3	-23.8	68.2	-20.4	-1	-6.1
598	TGGATTTAACCATTTCCTCA SEQ ID NO:1499	-2.3	-22.5	65.5	-19.4	-0.6	-4.3
820	CATTCGAATATTTAACAAAC SEQ ID NO:1500	-2.3	-14.5	47.9	-11.4	0	-9.3
853	TTACTATACACACACATTTA SEQ ID NO:1501	-2.3	-17.8	56.1	-15.5	0	-1.7
947	TGACTCACTGCGGTCTTCAG SEQ ID NO:1502	-2.3	-25.4	73.8	-22.1	-0.9	-6.2
1118	TTCCCAAAGCCAAAAAAAAA SEQ ID NO:1503	-2.3	-16.7	50.3	-14.4	0	-3.2
1242	CCGGGAACTACATCAGCAGC SEQ ID NO:1504	-2.3	-26.2	72.1	-23.4	-0.2	-5.6
1398	TTATAAAAATATATAAATAT SEQ ID NO:1505	-2.3	-8.1	36.2	-5.3	-0.1	-4.2
1669	ACTTATTTTCATACCTTAAA SEQ ID NO:1506	-2.3	-17.5	55.2	-15.2	0	-2.3
1672	AAAACTTATTTTCATACCTT SEQ ID NO:1507	-2.3	-17.1	53.9	-14.1	-0.4	-2.9
1729	ATTTTAAAGTTGACATGTTT SEQ ID NO:1508	-2.3	-16.8	54.3	-14.5	0	-7.1
1860	AATACTGAAATAATTCTTAA SEQ ID NO:1509	-2.3	-12.8	45.1	-9.3	-1.1	-4.2
1939	CTTATGCAGCTTTACATTCA SEQ ID NO:1510	-2.3	-21.9	66	-19.6	0	-5.5
49	GTTTCCCAGCTGCCTCCGGC SEQ ID NO:1511	-2.2	-34.1	89.7	-30.5	-1.3	-8.1
287	CCGGGCCACACTTCATGCCA SEQ ID NO:1512	-2.2	-31.4	80.9	-27	-2.2	-7.6
501	TCCGTGAGAGAAACAAATCT SEQ ID NO:1513	-2.2	-19.6	58	-17.4	0	-2.9
599	GTGGATTTAACCATTTCCTC SEQ ID NO:1514	-2.2	-23	67.5	-19.9	-0.8	-4.8
726	ATCACAATTTGGATCTTCAA SEQ ID NO:1515	-2.2	-19.1	58.8	-16.9	0	-5.2
855	TGTTACTATACACACACATT SEQ ID NO:1516	-2.2	-19.2	59.3	-17	0	-2.6

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
968	ATCAAAGTCAAAGAACTAAT SEQ ID NO:1517	-2.2	-14.6	48.5	-12.4	0	-3
1309	GTTAAAGCTATTTATGGAAG SEQ ID NO:1518	-2.2	-17	54.3	-14.2	-0.3	-4.6
1315	GCATACGTTAAAGCTATTTA SEQ ID NO:1519	-2.2	-19.1	58.2	-16.4	-0.1	-5.7
1445	GGATGATAAATATGGGTAGG SEQ ID NO:1520	-2.2	-18.9	57.9	-16.7	0	-2.7
1556	TAATTATGGATAATAAATTT SEQ ID NO:1521	-2.2	-12.1	43.7	-9.3	-0.3	-5.2
1799	CTAAGAACATCTAGTACAAC SEQ ID NO:1522	-2.2	-17	54.2	-14.8	0	-5.7
80	GGAGCGTGGTCAGCAGCAAG SEQ ID NO:1523	-2.1	-27.4	77.4	-23.7	-1.5	-5.9
104	CGGCCACCAGGTGTGCAGGC SEQ ID NO:1524	-2.1	-32.5	86.1	-27.8	-2.5	-12.5
650	GAACAATCACGAAAATAGAG SEQ ID NO:1525	-2.1	-15	48.6	-12.9	0	-3.5
1078	TAGAGAAGCTACCTACCAAG SEQ ID NO:1526	-2.1	-21.6	63.2	-19.5	0	-5.1
1924	ATTCAAAGGCCTTCCACACA SEQ ID NO:1527	-2.1	-24.7	69.1	-21.3	-1	-10.1
145	ACAGTGTTGAGGGCAGTCCA SEQ ID NO:1528	-2	-27.2	79.2	-24.1	-1	-6.6
171	GGGCTGCTTTTGCACTCACT SEQ ID NO:1529	-2	-27.9	79.7	-23.8	-2.1	-8.4
258	GAGACTGTGCGGTAGCAAGT SEQ ID NO:1530	-2	-25.2	72.8	-20.5	-2.7	-7
514	TGCCATGTCATGCTCCGTGA SEQ ID NO:1531	-2	-28.5	78.2	-25.6	-0.7	-5.7
625	TCTCAGAAATCACAGCCGGG SEQ ID NO:1532	-2	-24.6	68.8	-22.6	0	-6.9
1311	ACGTTAAAGCTATTTATGGA SEQ ID NO:1533	-2	-18.7	57.3	-16.1	-0.3	-5.7
1382	ATATTTACCTTCATACACAC SEQ ID NO:1534	-2	-19.6	60	-17.6	0	-1.8
1399	TTTATAAAAATATATAAATA SEQ ID NO:1535	-2	-8.2	36.4	-5.3	-0.8	-5.5
1404	ATTTATTTATAAAAATATAT SEQ ID NO:1536	-2	-10.1	39.9	-6.8	-1.2	-6
1480	TTTCAACAAATAATACTAGA SEQ ID NO:1537	-2	-14.2	47.9	-12.2	0	-4.5
1956	AAAACAAAACCTAACAGCTT SEQ ID NO:1538	-2	-16.5	51.1	-14.5	0	-4.5
497	TGAGAGAAACAAATCTGTTG SEQ ID NO:1539	-1.9	-16.5	52.6	-13	-1.5	-4.5
513	GCCATGTCATGCTCCGTGAG SEQ ID NO:1540	-1.9	-28.5	78.7	-25.6	-0.9	-6.6
614	ACAGCCGGGATCAGCGTGGA SEQ ID NO:1541	-1.9	-29.2	78.1	-26.4	-0.7	-6.9
672	CCTAAAATGTTGGCTGTGTG SEQ ID NO:1542	-1.9	-22.1	64.3	-20.2	0	-3.9
981	AACATTAATGTACATCAAAG SEQ ID NO:1543	-1.9	-14.8	49	-11.6	-0.2	-10.5
1852	AATAATTCTTAAATAAGTTC SEQ ID NO:1544	-1.9	-12.8	45.5	-10.9	0	-4.9
1893	CTGTTGGCCAACTTCAAGAA SEQ ID NO:1545	-1.9	-22.7	65.2	-17.4	-0.5	-15
1951	AAAACCTAACAGCTTATGCA SEQ ID NO:1546	-1.9	-19.9	58.5	-16.4	-1.6	-5.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
219	CACACTCGGCAGCAGCCACA SEQ ID NO:1547	-1.8	-29.5	79	-24.5	-3.2	-9.8
428	CCGTCCCCCTGTCACAGATG SEQ ID NO:1548	-1.8	-31.1	81.2	-28.7	-0.3	-5.2
616	TCACAGCCGGGATCAGCGTG SEQ ID NO:1549	-1.8	-28.5	77	-25.1	-1.6	-8.1
806	ACAAACACATACAAGTGTTC SEQ ID NO:1550	-1.8	-18.1	56.3	-13.5	-2.8	-8.2
819	ATTCGAATATTTAACAAACA SEQ ID NO:1551	-1.8	-14.5	47.9	-12	0	-9.1
1050	AAATATTTTATTTCCCACTC SEQ ID NO:1552	-1.8	-19.1	58.4	-16.7	-0.3	-5.8
1310	CGTTAAAGCTATTTATGGAA SEQ ID NO:1553	-1.8	-17.8	54.9	-15.4	-0.3	-5.1
1953	ACAAAACCTAACAGCTTATG SEQ ID NO:1554	-1.8	-18.3	55.4	-16.5	0	-4.5
85	CACGAGGAGCGTGGTCAGCA SEQ ID NO:1555	-1.7	-27.9	76.9	-23.4	-2.8	-9.7
101	CCACCAGGTGTGCAGGCACG SEQ ID NO:1556	-1.7	-30.4	80.9	-26.2	-2.5	-11.6
311	CATTAGAAGGCTGACACCTC SEQ ID NO:1557	-1.7	-23.3	67.7	-20.8	-0.6	-4.3
375	ATCCCGAAGGTGCCGTAGGG SEQ ID NO:1558	-1.7	-29.4	77.2	-25	-2.7	-7.9
1156	CTTCCTTCAGGGGTTTTCTG SEQ ID NO:1559	-1.7	-25.9	76.6	-23.6	-0.3	-5.7
1159	TTACTTCCTTCAGGGGTTTT SEQ ID NO:1560	-1.7	-24.6	73.3	-22.4	-0.2	-4.7
1287	TATGTGTTTCCTATGCCCCA SEQ ID NO:1561	-1.7	-27.8	76.9	-26.1	0	-3
1401	TATTTATAAAAATATATAAA SEQ ID NO:1562	-1.7	-8.2	36.4	-5.3	-1.1	-6.5
1474	CAAATAATACTAGATTTCTT SEQ ID NO:1563	-1.7	-15	49.9	-13.3	0	-4.5
1568	GAGTGACTCCTATAATTATG SEQ ID NO:1564	-1.7	-19.3	59.6	-17.6	0	-5.9
1874	ATAAAATACAGGTAAATACT SEQ ID NO:1565	-1.7	-13.7	46.7	-12	0	-3.8
427	CGTCCCCCTGTCACAGATGC SEQ ID NO:1566	-1.6	-30.9	82.1	-28.7	-0.3	-5.2
1072	AGCTACCTACCAAGGAAGGG SEQ ID NO:1567	-1.6	-24.9	69.6	-22.4	-0.7	-8.8
1083	AATTCTAGAGAAGCTACCTA SEQ ID NO:1568	-1.6	-20.1	61.2	-18.5	0	-5.8
1299	TTTATGGAAGTGTATGTGTT SEQ ID NO:1569	-1.6	-19.6	61.6	-18	0	-1.3
1383	AATATTTACCTTCATACACA SEQ ID NO:1570	-1.6	-18.7	57.5	-17.1	0	-3.8
1397	TATAAAAATATATAAATATT SEQ ID NO:1571	-1.6	-8.1	36.2	-5.3	-1.1	-4.4
1580	TTTTGAAATCCAGAGTGACT SEQ ID NO:1572	-1.6	-20.1	60.8	-18.5	0	-4.2
1742	TAATTCCACCTATATTTTAA SEQ ID NO:1573	-1.6	-18	55.7	-16.4	0	-2.9
256	GACTGTGCGGTAGCAAGTTT SEQ ID NO:1574	-1.5	-24.8	71.9	-20.4	-2.9	-7.2
259	TGAGACTGTGCGGTAGCAAG SEQ ID NO:1575	-1.5	-24	69.3	-20.5	-2	-7
407	CTGACTGGCAGTTGCAGGTC SEQ ID NO:1576	-1.5	-26.9	78.8	-24.4	-0.9	-7.6

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
519	CCAGATGCCATGTCATGCTC SEQ ID NO:1577	-1.5	-27.2	76.6	-25.2	-0.2	-4.6
620	GAAATCACAGCCGGGATCAG SEQ ID NO:1578	-1.5	-23.9	66.8	-22.4	0	-6.9
659	CTGTGTGTTGAACAATCACG SEQ ID NO:1579	-1.5	-20.8	61.5	-17.4	-1.9	-8.7
1058	GAAGGGCTAAATATTTTATT SEQ ID NO:1580	-1.5	-17.1	54.2	-15.6	0	-6.2
1158	TACTTCCTTCAGGGGTTTTC SEQ ID NO:1581	-1.5	-24.9	74.8	-23.4	0.4	-4.1
1295	TGGAAGTGTATGTGTTTCCT SEQ ID NO:1582	-1.5	-23.1	69.5	-19.9	-1.7	-5.4
1300	ATTTATGGAAGTGTATGTGT SEQ ID NO:1583	-1.5	-19.5	61.2	-18	0	-1.8
1313	ATACGTTAAAGCTATTTATG SEQ ID NO:1584	-1.5	-16.6	53	-14.5	-0.3	-5.7
1681	AACCTCCTAAAAACTTATTT SEQ ID NO:1585	-1.5	-17.7	54.1	-16.2	0	-2.2
1814	CTTCTGAGATATTTCCTAAG SEQ ID NO:1586	-1.5	-19.7	60.9	-18.2	0	-3.3
1947	CCTAACAGCTTATGCAGCTT SEQ ID NO:1587	-1.5	-24.6	70.5	-21.1	-2	-6.9
1948	ACCTAACAGCTTATGCAGCT SEQ ID NO:1588	-1.5	-24.7	70.7	-21.3	-1.9	-6.9
698	TGTACTTATGCTATATCTAG SEQ ID NO:1589	-1.4	-18.9	60.1	-17.5	0	-4.8
978	ATTAATGTACATCAAAGTCA SEQ ID NO:1590	-1.4	-16.9	54.1	-14.9	0	-8.4
1073	AAGCTACCTACCAAGGAAGG SEQ ID NO:1591	-1.4	-23	65.1	-20	-1.6	-9.2
1288	GTATGTGTTTCCTATGCCCC SEQ ID NO:1592	-1.4	-28.3	79.3	-26.9	0	-3
1384	AAATATTTACCTTCATACAC SEQ ID NO:1593	-1.4	-17.3	54.5	-15.9	0	-5.8
1570	CAGAGTGACTCCTATAATTA SEQ ID NO:1594	-1.4	-20	61.2	-17.9	-0.4	-5.5
1749	ATACTCCTAATTCCACCTAT SEQ ID NO:1595	-1.4	-23.1	66.4	-21.7	0	-2.9
1751	ATATACTCCTAATTCCACCT SEQ ID NO:1596	-1.4	-23.1	66.4	-21.7	0	-2.9
1825	CAAATAAAATACTTCTGAGA SEQ ID NO:1597	-1.4	-14.3	47.9	-12.9	0	-2.8
1861	AAATACTGAAATAATTCTTA SEQ ID NO:1598	-1.4	-12.8	45.1	-10.2	-1.1	-4.2
1892	TGTTGGCCAACTTCAAGAAT SEQ ID NO:1599	-1.4	-21.8	63.4	-17	-0.5	-15
1938	TTATGCAGCTTTACATTCAA SEQ ID NO:1600	-1.4	-20.3	61.8	-18.9	0	-5.5
86	GCACGAGGAGCGTGGTCAGC SEQ ID NO:1601	-1.3	-29	80.2	-24.2	-3.5	-9.7
167	TGCTTTTGCACTCACTGCTG SEQ ID NO:1602	-1.3	-25.5	73.9	-22.2	-2	-7.5
1456	TTTCCTCAAGAGGATGATAA SEQ ID NO:1603	-1.3	-19.9	60.3	-17	-1.5	-10.2
1460	TTTCTTTCCTCAAGAGGATG SEQ ID NO:1604	-1.3	-21.8	65.8	-18.9	-1.5	-10.2
1470	TAATACTAGATTTCTTTCCT SEQ ID NO:1605	-1.3	-19.1	59.8	-17.8	0	-4
1725	TAAAGTTGACATGTTTTCTG SEQ ID NO:1606	-1.3	-17.9	56.9	-16.6	0	-7.1

position	oligo	kcal/ mol total binding	kcal/ mol duplex form-ation	deg C Tm of Duplex	kcal/ mol target struc-ture	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
499	CGTGAGAGAAACAAATCTGT SEQ ID NO:1607	-1.2	-18.4	55.9	-16.6	-0.3	-3.3
834	AACAAATCTACATGCATTCG SEQ ID NO:1608	-1.2	-18.5	55.9	-17.3	0	-6.7
1067	CCTACCAAGGAAGGGCTAAA SEQ ID NO:1609	-1.2	-23.3	64.7	-21.2	-0.7	-5.1
1071	GCTACCTACCAAGGAAGGGC SEQ ID NO:1610	-1.2	-26.7	73.4	-23.9	-1.6	-6.1
1085	TAAATTCTAGAGAAGCTACC SEQ ID NO:1611	-1.2	-18.5	57.3	-17.3	0	-5.6
1157	ACTTCCTTCAGGGGTTTTCT SEQ ID NO:1612	-1.2	-26.1	77.5	-24.4	-0.2	-5.7
1161	TCTTACTTCCTTCAGGGGTT SEQ ID NO:1613	-1.2	-25.7	76.5	-24	-0.2	-4.7
1178	TCCATAAGCTTCAAACATCT SEQ ID NO:1614	-1.2	-20.8	61.7	-19.6	0	-6.5
1179	TTCCATAAGCTTCAAACATC SEQ ID NO:1615	-1.2	-20	60.2	-18.8	0	-6.8
1308	TTAAAGCTATTTATGGAAGT SEQ ID NO:1616	-1.2	-17	54.3	-15.2	-0.3	-5.1
1312	TACGTTAAAGCTATTTATGG SEQ ID NO:1617	-1.2	-17.8	55.5	-16.6	0	-5.7
1387	TATAAATATTTACCTTCATA SEQ ID NO:1618	-1.2	-15.6	51.1	-13.9	0	-7.9
1856	CTGAAATAATTCTTAAATAA SEQ ID NO:1619	-1.2	-11.9	43.3	-9.5	-1.1	-4.2
1940	GCTTATGCAGCTTTACATTC SEQ ID NO:1620	-1.2	-23	69.2	-20.6	-1.1	-6.1
498	GTGAGAGAAACAAATCTGTT SEQ ID NO:1621	-1.1	-17.7	55.5	-15.2	-1.3	-4.3
654	TGTTGAACAATCACGAAAAT SEQ ID NO:1622	-1.1	-16	50.4	-14.1	-0.6	-4.4
1241	CGGGAACTACATCAGCAGCC SEQ ID NO:1623	-1.1	-26.2	72.1	-24.6	-0.2	-4.7
1396	ATAAAAATATATAAATATTT SEQ ID NO:1624	-1.1	-8.5	36.9	-5.3	-2.1	-6
1674	TAAAAACTTATTTTCATACC SEQ ID NO:1625	-1.1	-15.1	49.6	-13	-0.9	-3.3
1937	TATGCAGCTTTACATTCAAA SEQ ID NO:1626	-1.1	-19.5	59.4	-18.4	0	-5.5
103	GGCCACCAGGTGTGCAGGCA SEQ ID NO:1627	-1	-32.4	87.9	-28.5	-2.9	-12.5
179	TGCAGCGCGGGCTGCTTTTG SEQ ID NO:1628	-1	-29.8	79.8	-22.6	-6.2	-16.3
339	CCAAACTCTTCACCAAAAGG SEQ ID NO:1629	-1	-20.9	59.8	-19.9	0	-3.6
511	CATGTCATGCTCCGTGAGAG SEQ ID NO:1630	-1	-25.3	72.4	-23.3	-0.9	-6.5
711	TTCAAAAATTACATGTACTT SEQ ID NO:1631	-1	-15.2	50	-13.7	0	-7.7
852	TACTATACACACACATTTAA SEQ ID NO:1632	-1	-17	53.9	-16	0	-2.2
1752	AATATACTCCTAATTCCACC SEQ ID NO:1633	-1	-21.5	62.5	-20.5	0	-2.9
313	CCCATTAGAAGGCTGACACC SEQ ID NO:1634	-0.9	-26	71.3	-25.1	0	-3.7
653	GTTGAACAATCACGAAAATA SEQ ID NO:1635	-0.9	-15.7	49.9	-14	-0.6	-4.4
979	CATTAATGTACATCAAAGTC SEQ ID NO:1636	-0.9	-16.9	54.1	-15.5	0	-7.9

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1096	AAAAGCACAATTAAATTCTA SEQ ID NO:1637	-0.9	-14.1	47.3	-13.2	0	-4.1
1286	ATGTGTTTCCTATGCCCCAG SEQ ID NO:1638	-0.9	-28.1	77.8	-27.2	0	-3
1293	GAAGTGTATGTGTTTCCTAT SEQ ID NO:1639	-0.9	-21.6	66.3	-20.7	0	-2.2
1748	TACTCCTAATTCCACCTATA SEQ ID NO:1640	-0.9	-22.8	65.9	-21.9	0	-2.9
1750	TATACTCCTAATTCCACCTA SEQ ID NO:1641	-0.9	-22.8	65.9	-21.9	0	-2.9
1919	AAGGCCTTCCACACACATTC SEQ ID NO:1642	-0.9	-25.6	71.9	-23.4	-1	-9.8
374	TCCCGAAGGTGCCGTAGGGA SEQ ID NO:1643	-0.8	-30	78.4	-26.5	-2.7	-9.3
405	GACTGGCAGTTGCAGGTCTC SEQ ID NO:1644	-0.8	-27.3	81	-25.5	-0.9	-7.7
1521	TTTGAAAACCTTATAGAGTC SEQ ID NO:1645	-0.8	-17.5	55.3	-16.7	0	-3.5
1997	TCTTGTTCTTTTTTATTGAA SEQ ID NO:1646	-0.8	-18.2	58.6	-17.4	0	-3.3
357	GGACAGTCTTTGCAGATACC SEQ ID NO:1647	-0.7	-24.4	71.8	-23.2	-0.2	-6
1294	GGAAGTGTATGTGTTTCCTA SEQ ID NO:1648	-0.7	-22.8	69.1	-21	-1	-4.6
1457	CTTTCCTCAAGAGGATGATA SEQ ID NO:1649	-0.7	-21.5	64.3	-19.2	-1.5	-10.2
1557	ATAATTATGGATAATAAATT SEQ ID NO:1650	-0.7	-12	43.5	-10.7	-0.3	-5.3
1569	AGAGTGACTCCTATAATTAT SEQ ID NO:1651	-0.7	-19.3	59.9	-17.9	-0.4	-5.9
288	CCCGGGCCACACTTCATGCC SEQ ID NO:1652	-0.6	-32.7	83.1	-30.9	-1.1	-9.2
559	ATTCTCTTTCACAACTTCTT SEQ ID NO:1653	-0.6	-20.8	64.5	-20.2	0	-1
710	TCAAAAATTACATGTACTTA SEQ ID NO:1654	-0.6	-14.8	49.2	-13.7	0	-7.7
1097	AAAAAGCACAATTAAATTCT SEQ ID NO:1655	-0.6	-13.7	46.4	-13.1	0	-3.3
1323	CTGAGGTGGCATACGTTAAA SEQ ID NO:1656	-0.6	-21.9	63.6	-21.3	0.5	-4.8
1385	TAAATATTTACCTTCATACA SEQ ID NO:1657	-0.6	-16.8	53.4	-16.2	0	-7
1730	TATTTTAAAGTTGACATGTT SEQ ID NO:1658	-0.6	-16.4	53.4	-15.8	0	-7.1
1747	ACTCCTAATTCCACCTATAT SEQ ID NO:1659	-0.6	-23.1	66.4	-22.5	0	-2.9
1770	TGTGCTAAGATTCTTTCAAA SEQ ID NO:1660	-0.6	-18.8	58.4	-17.7	-0.1	-5.6
1819	AAATACTTCTGAGATATTTC SEQ ID NO:1661	-0.6	-16.3	53.4	-14.8	-0.7	-4.6
1826	TCAAATAAAATACTTCTGAG SEQ ID NO:1662	-0.6	-14.1	47.7	-13.5	0	-2.8
1828	CTTCAAATAAAATACTTCTG SEQ ID NO:1663	-0.6	-14.5	48.5	-13.9	0	-1.5
1936	ATGCAGCTTTACATTCAAAG SEQ ID NO:1664	-0.6	-19.8	60.2	-18.7	-0.2	-5.8
168	CTGCTTTTGCACTCACTGCT SEQ ID NO:1665	-0.5	-26.4	76.1	-23.8	-2.1	-7.6
184	CCTCTTGCAGCGCGGGCTGC SEQ ID NO:1666	-0.5	-32.9	86.1	-27	-5.4	-15.3

position	oligo	kcal/ mol total binding	kcal/ mol duplex form-ation	deg C Tm of Duplex	kcal/ mol target struc-ture	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
307	AGAAGGCTGACACCTCAGCC SEQ ID NO:1667	-0.5	-27.3	76	-21.1	-5.7	-13
408	CCTGACTGGCAGTTGCAGGT SEQ ID NO:1668	-0.5	-28.5	80.6	-26.1	-1.9	-9
613	CAGCCGGGATCAGCGTGGAT SEQ ID NO:1669	-0.5	-29	77.5	-27.6	-0.7	-6.9
980	ACATTAATGTACATCAAAGT SEQ ID NO:1670	-0.5	-16.7	53.4	-15.3	0	-9.6
1070	CTACCTACCAAGGAAGGGCT SEQ ID NO:1671	-0.5	-25.8	71.2	-23.7	-1.6	-6.6
1090	ACAATTAAATTCTAGAGAAG SEQ ID NO:1672	-0.5	-14.2	48.1	-13.7	0	-5.8
1240	GGGAACTACATCAGCAGCCT SEQ ID NO:1673	-0.5	-26.3	74	-25.3	-0.2	-4.7
1296	ATGGAAGTGTATGTGTTTCC SEQ ID NO:1674	-0.5	-22.2	67.4	-20.7	-0.9	-4.4
1876	GAATAAAATACAGGTAAATA SEQ ID NO:1675	-0.5	-12.5	44.3	-12	0	-3.6
93	TGTGCAGGCACGAGGAGCGT SEQ ID NO:1676	-0.4	-28.6	78.3	-26.6	-1.3	-10.7
846	ACACACACATTTAACAAATC SEQ ID NO:1677	-0.4	-16.7	52.7	-16.3	0	-2.7
1768	TGCTAAGATTCTTTCAAATA SEQ ID NO:1678	-0.4	-17.3	55	-16.4	-0.1	-5.6
1932	AGCTTTACATTCAAAGGCCT SEQ ID NO:1679	-0.4	-23.2	67.3	-22	-0.6	-8.4
1946	CTAACAGCTTATGCAGCTTT SEQ ID NO:1680	-0.4	-22.7	67.1	-20.5	-1.8	-6.9
1949	AACCTAACAGCTTATGCAGC SEQ ID NO:1681	-0.4	-23.1	66.5	-21.1	-1.6	-5.7
65	GCAAGACGCTCTTCATGTTT SEQ ID NO:1682	-0.3	-24	69.7	-22.9	-0.6	-6.1
558	TTCTCTTTCACAACTTCTTC SEQ ID NO:1683	-0.3	-21.2	66.1	-20.9	0	-0.7
610	CCGGGATCAGCGTGGATTTA SEQ ID NO:1684	-0.3	-26.4	72.3	-26.1	0	-7
712	CTTCAAAAATTACATGTACT SEQ ID NO:1685	-0.3	-16	51.6	-15.2	0	-7.7
723	ACAATTTGGATCTTCAAAAA SEQ ID NO:1686	-0.3	-15.9	51	-14.2	-1.3	-6.3
506	CATGCTCCGTGAGAGAAACA SEQ ID NO:1687	-0.2	-23.1	65.3	-21.8	-1	-6.1
701	ACATGTACTTATGCTATATC SEQ ID NO:1688	-0.2	-19.2	60.3	-19	0	-6.1
825	ACATGCATTCGAATATTTAA SEQ ID NO:1689	-0.2	-17.5	54.2	-16.7	0	-8.4
845	CACACACATTTAACAAATCT SEQ ID NO:1690	-0.2	-17.4	54	-17.2	0	-2.7
1459	TTCTTTCCTCAAGAGGATGA SEQ ID NO:1691	-0.2	-22.3	66.8	-20.7	-1.2	-9.9
1467	TACTAGATTTCTTTCCTCAA SEQ ID NO:1692	-0.2	-20.5	63.1	-20.3	0	-4.5
1673	AAAAACTTATTTTCATACCT SEQ ID NO:1693	-0.2	-16.3	52	-15.1	-0.9	-3.3
1769	GTGCTAAGATTCTTTCAAAT SEQ ID NO:1694	-0.2	-18.8	58.5	-18.1	-0.1	-5.5
1853	AAATAATTCTTAAATAAGTT SEQ ID NO:1695	-0.2	-11.7	43.1	-11.5	0	-4.9
655	GTGTTGAACAATCACGAAAA SEQ ID NO:1696	-0.1	-17.2	52.9	-16.3	-0.6	-8.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
722	CAATTTGGATCTTCAAAAAT SEQ ID NO:1697	-0.1	-15.7	50.6	-14.2	-1.3	-6.3
962	GTCAAAGAACTAATTTGACT SEQ ID NO:1698	-0.1	-16.8	53.4	-13.3	-3.4	-9.4
969	CATCAAAGTCAAAGAACTAA SEQ ID NO:1699	-0.1	-15.3	49.8	-15.2	0	-3
1117	TCCCAAAGCCAAAAAAAAAA SEQ ID NO:1700	-0.1	-15.9	48.7	-15.8	0	-3.2
1324	TCTGAGGTGGCATACGTTAA SEQ ID NO:1701	-0.1	-23	67.2	-22.3	-0.3	-4.8
1875	AATAAAATACAGGTAAATAC SEQ ID NO:1702	-0.1	-12.1	43.5	-12	0	-3.6
1935	TGCAGCTTTACATTCAAAGG SEQ ID NO:1703	-0.1	-21	62.7	-20.9	0.1	-7.6
1292	AAGTGTATGTGTTTCCTATG SEQ ID NO:1704	0	-21	64.7	-21	0	-1.7
1682	AAACCTCCTAAAAACTTATT SEQ ID NO:1705	0	-16.9	52.2	-16.9	0	-1.3
1827	TTCAAATAAAATACTTCTGA SEQ ID NO:1706	0	-14.2	47.9	-14.2	0	-2.5
512	CCATGTCATGCTCCGTGAGA SEQ ID NO:1707	0.1	-27.3	75.7	-26.7	-0.4	-6.6
1094	AAGCACAATTAAATTCTAGA SEQ ID NO:1708	0.1	-16.1	51.8	-16.2	0	-5.4
1162	ATCTTACTTCCTTCAGGGGT SEQ ID NO:1709	0.1	-25.6	76	-25.2	-0.2	-4.7
1307	TAAAGCTATTTATGGAAGTG SEQ ID NO:1710	0.1	-16.9	54	-17	0	-5.1
1481	TTTTCAACAAATAATACTAG SEQ ID NO:1711	0.1	-13.7	47	-13.8	0	-4
1923	TTCAAAGGCCTTCCACACAC SEQ ID NO:1712	0.1	-24.9	69.7	-23.5	-1	-10.6
1967	CATGTCCTTTTAAAACAAAA SEQ ID NO:1713	0.1	-15.9	50.5	-15.5	-0.1	-6.2
89	CAGGCACGAGGAGCGTGGTC SEQ ID NO:1714	0.2	-28.4	78.4	-25.1	-3.5	-9
257	AGACTGTGCGGTAGCAAGTT SEQ ID NO:1715	0.2	-24.7	71.8	-22	-2.9	-7.2
652	TTGAACAATCACGAAAATAG SEQ ID NO:1716	0.2	-14.5	47.6	-13.9	-0.6	-4.4
1068	ACCTACCAAGGAAGGGCTAA SEQ ID NO:1717	0.2	-24.2	67.3	-22.8	-1.6	-6.6
1084	AAATTCTAGAGAAGCTACCT SEQ ID NO:1718	0.2	-19.7	59.7	-19.9	0	-5.8
1169	TTCAAACATCTTACTTCCTT SEQ ID NO:1719	0.2	-20.4	61.8	-20.6	0	-1
1177	CCATAAGCTTCAAACATCTT SEQ ID NO:1720	0.2	-20.5	60.7	-20.7	0	-6.8
1392	AAATATATAAATATTTACCT SEQ ID NO:1721	0.2	-13	45.4	-11.4	-1.8	-7.9
1476	AACAAATAATACTAGATTTC SEQ ID NO:1722	0.2	-13.5	46.7	-13.7	0	-4.5
1741	AATTCCACCTATATTTTAAA SEQ ID NO:1723	0.2	-17.6	54.5	-17.8	0	-4.2
1877	AGAATAAAATACAGGTAAAT SEQ ID NO:1724	0.2	-12.8	44.8	-13	0	-3.6
807	AACAAACACATACAAGTGTT SEQ ID NO:1725	0.3	-17	53.3	-14.7	-2.6	-8
1053	GCTAAATATTTTATTTCCCA SEQ ID NO:1726	0.3	-20	59.9	-19.5	-0.6	-6.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1059	GGAAGGGCTAAATATTTTAT SEQ ID NO:1727	0.3	-18.2	56.3	-18.5	0	-6.6
1074	GAAGCTACCTACCAAGGAAG SEQ ID NO:1728	0.3	-22.4	63.9	-21.1	-1.6	-9.2
1391	AATATATAAATATTTACCTT SEQ ID NO:1729	0.3	-13.8	47.1	-13.2	-0.8	-7.9
1455	TTCCTCAAGAGGATGATAAA SEQ ID NO:1730	0.3	-19.1	58.1	-17.8	-1.5	-10.2
1468	ATACTAGATTTCTTTCCTCA SEQ ID NO:1731	0.3	-21.2	65.3	-21.5	0	-4.5
88	AGGCACGAGGAGCGTGGTCA SEQ ID NO:1732	0.4	-28.4	78.4	-25.3	-3.5	-9.2
221	CGCACACTCGGCAGCAGCCA SEQ ID NO:1733	0.4	-31.2	81.2	-28.4	-3.2	-9.8
224	CAGCGCACACTCGGCAGCAG SEQ ID NO:1734	0.4	-29.2	78.2	-27.3	-2.3	-8.5
861	CTTCAGTGTTACTATACACA SEQ ID NO:1735	0.4	-20.6	63.8	-19.4	-1.5	-5.7
977	TTAATGTACATCAAAGTCAA SEQ ID NO:1736	0.4	-16.2	52.3	-16	0	-8.4
1069	TACCTACCAAGGAAGGGCTA SEQ ID NO:1737	0.4	-24.6	68.8	-23.4	-1.6	-6.6
1173	AAGCTTCAAACATCTTACTT SEQ ID NO:1738	0.4	-19	58.5	-19.4	0	-6.2
1322	TGAGGTGGCATACGTTAAAG SEQ ID NO:1739	0.4	-21	62	-20.8	-0.3	-4.8
1475	ACAAATAATACTAGATTTCT SEQ ID NO:1740	0.4	-15.1	50.1	-15.5	0	-4.5
1813	TTCTGAGATATTTCCTAAGA SEQ ID NO:1741	0.4	-19.4	60.3	-19.8	0	-4.6
176	AGCGCGGGCTGCTTTTGCAC SEQ ID NO:1742	0.5	-30	80.6	-27.2	-3.3	-12.5
178	GCAGCGCGGGCTGCTTTTGC SEQ ID NO:1743	0.5	-31.6	84.2	-26.6	-5.5	-15.5
418	GTCACAGATGCCTGACTGGC SEQ ID NO:1744	0.5	-27.2	77.4	-25.6	-2.1	-8.7
505	ATGCTCCGTGAGAGAAACAA SEQ ID NO:1745	0.5	-21.7	62.2	-21.1	-1	-6.1
507	TCATGCTCCGTGAGAGAAAC SEQ ID NO:1746	0.5	-22.8	65.6	-22.6	-0.4	-5.9
891	TGTAAGATTACCTAAATTGC SEQ ID NO:1747	0.5	-17.9	55.6	-18.4	0	-4.9
892	ATGTAAGATTACCTAAATTG SEQ ID NO:1748	0.5	-16.1	51.8	-16.6	0	-4.9
1405	CATTTATTTATAAAAATATA SEQ ID NO:1749	0.5	-10.8	41.3	-10	-1.2	-6.5
1447	GAGGATGATAAATATGGGTA SEQ ID NO:1750	0.5	-18.3	56.7	-18.8	0	-2.7
1469	AATACTAGATTTCTTTCCTC SEQ ID NO:1751	0.5	-19.8	61.8	-20.3	0	-4.5
1824	AAATAAAATACTTCTGAGAT SEQ ID NO:1752	0.5	-13.6	46.6	-14.1	0	-2.8
7	TGCTGGTGGGAAGCAGCCGT SEQ ID NO:1753	0.6	-29.7	80.5	-27.4	-2.9	-8.4
220	GCACACTCGGCAGCAGCCAC SEQ ID NO:1754	0.6	-30.6	82.3	-28	-3.2	-9.8
281	CACACTTCATGCCATCCATG SEQ ID NO:1755	0.6	-25.5	71.3	-24.5	-1.6	-4.7
500	CCGTGAGAGAAACAAATCTG SEQ ID NO:1756	0.6	-19.2	56.7	-19.8	0	-3.1

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1092	GCACAATTAAATTCTAGAGA SEQ ID NO:1757	0.6	-17.4	54.8	-18	0	-5.8
1095	AAAGCACAATTAAATTCTAG SEQ ID NO:1758	0.6	-14.8	49	-15.4	0	-4.1
1301	TATTTATGGAAGTGTATGTG SEQ ID NO:1759	0.6	-18	57.4	-18.6	0	-1.8
1466	ACTAGATTTCTTTCCTCAAG SEQ ID NO:1760	0.6	-20.8	63.9	-21.4	0	-4.5
1764	AAGATTCTTTCAAATATACT SEQ ID NO:1761	0.6	-15.7	51.6	-15.8	-0.1	-5.2
1089	CAATTAAATTCTAGAGAAGC SEQ ID NO:1762	0.7	-15.8	51.4	-16.5	0	-5.8
1934	GCAGCTTTACATTCAAAGGC SEQ ID NO:1763	0.7	-22.8	67	-22.7	-0.6	-4.5
1950	AAACCTAACAGCTTATGCAG SEQ ID NO:1764	0.7	-20.6	60.6	-19.7	-1.6	-5.7
504	TGCTCCGTGAGAGAAACAAA SEQ ID NO:1765	0.8	-21	60.4	-20.7	-1	-6.1
963	AGTCAAAGAACTAATTTGAC SEQ ID NO:1766	0.8	-15.9	51.7	-13.3	-3.4	-9.4
1168	TCAAACATCTTACTTCCTTC SEQ ID NO:1767	0.8	-20.7	62.9	-21.5	0	-1
1298	TTATGGAAGTGTATGTGTTT SEQ ID NO:1768	0.8	-19.6	61.6	-20.4	0	-1.3
1306	AAAGCTATTTATGGAAGTGT SEQ ID NO:1769	0.8	-18.4	57.4	-19.2	0	-5.1
79	GAGCGTGGTCAGCAGCAAGA SEQ ID NO:1770	0.9	-26.8	76.2	-26.1	-1.5	-5.4
90	GCAGGCACGAGGAGCGTGGT SEQ ID NO:1771	0.9	-29.8	81	-27.9	-2.8	-10.3
651	TGAACAATCACGAAAATAGA SEQ ID NO:1772	0.9	-15	48.5	-15.2	-0.4	-4.4
725	TCACAATTTGGATCTTCAAA SEQ ID NO:1773	0.9	-18.4	56.9	-18.1	-1.1	-5.9
847	TACACACACATTTAACAAAT SEQ ID NO:1774	0.9	-16	51	-16.9	0	-2.5
1395	TAAAAATATATAAATATTTA SEQ ID NO:1775	0.9	-8.2	36.4	-6.8	-2.3	-7.6
409	GCCTGACTGGCAGTTGCAGG SEQ ID NO:1776	1	-29.1	81.5	-27.6	-2.5	-10.2
612	AGCCGGGATCAGCGTGGATT SEQ ID NO:1777	1	-28.4	76.8	-28.5	-0.7	-7.6
709	CAAAAATTACATGTACTTAT SEQ ID NO:1778	1	-14.4	48.2	-14.9	0	-7.7
1458	TCTTTCCTCAAGAGGATGAT SEQ ID NO:1779	1	-22.2	66.4	-21.6	-1.5	-10.2
1465	CTAGATTTCTTTCCTCAAGA SEQ ID NO:1780	1	-21.2	64.7	-21.3	-0.7	-6.8
1731	ATATTTTAAAGTTGACATGT SEQ ID NO:1781	1	-16.3	53.1	-17.3	0	-6.9
555	TCTTTCACAACTTCTTCTCT SEQ ID NO:1782	1.1	-22	67.8	-23.1	0	-0.7
851	ACTATACACACACATTTAAC SEQ ID NO:1783	1.1	-17.5	55	-18.6	0	-2.4
1812	TCTGAGATATTTCCTAAGAA SEQ ID NO:1784	1.1	-18.6	57.9	-19.7	0	-4.6
658	TGTGTGTTGAACAATCACGA SEQ ID NO:1785	1.2	-20.5	60.9	-19.8	-1.9	-8.7
1093	AGCACAATTAAATTCTAGAG SEQ ID NO:1786	1.2	-16.8	53.7	-18	0	-5.8

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
1394	AAAAATATATAAATATTTAC SEQ ID NO:1787	1.2	-8.7	37.3	-7.6	-2.3	-7.9
1477	CAACAAATAATACTAGATTT SEQ ID NO:1788	1.2	-13.8	46.9	-15	0	-4.5
1478	TCAACAAATAATACTAGATT SEQ ID NO:1789	1.2	-14.1	47.7	-15.3	0	-4.5
1479	TTCAACAAATAATACTAGAT SEQ ID NO:1790	1.2	-14.1	47.7	-15.3	0	-4.5
1740	ATTCCACCTATATTTTAAAG SEQ ID NO:1791	1.2	-18.3	56.4	-19.5	0	-4.6
306	GAAGGCTGACACCTCAGCCC SEQ ID NO:1792	1.3	-29.3	79.1	-24.5	-6.1	-13.4
604	TCAGCGTGGATTTAACCATT SEQ ID NO:1793	1.3	-22.9	65.8	-23.3	-0.8	-5.5
605	ATCAGCGTGGATTTAACCAT SEQ ID NO:1794	1.3	-22.8	65.5	-23.2	-0.8	-5.5
1454	TCCTCAAGAGGATGATAAAT SEQ ID NO:1795	1.3	-19	57.7	-18.9	-1.2	-9.7
611	GCCGGGATCAGCGTGGATTT SEQ ID NO:1796	1.4	-28.5	76.9	-29.4	0	-7.6
1393	AAAATATATAAATATTTACC SEQ ID NO:1797	1.4	-11.4	42.2	-10.5	-2.3	-7.9
1823	AATAAAATACTTCTGAGATA SEQ ID NO:1798	1.4	-14	47.7	-15.4	0	-2.8
1873	TAAAATACAGGTAAATACTG SEQ ID NO:1799	1.4	-13.7	46.7	-14.4	-0.5	-4
170	GGCTGCTTTTGCACTCACTG SEQ ID NO:1800	1.5	-26.7	76.8	-26.1	-2.1	-8.4
177	CAGCGCGGGCTGCTTTTGCA SEQ ID NO:1801	1.5	-30.5	81	-28.7	-3.3	-12.4
1077	AGAGAAGCTACCTACCAAGG SEQ ID NO:1802	1.5	-23.1	66.2	-23.3	-1.2	-6.9
1765	TAAGATTCTTTCAAATATAC SEQ ID NO:1803	1.5	-14.5	49.2	-15.5	-0.1	-5.6
144	CAGTGTTGAGGGCAGTCCAC SEQ ID NO:1804	1.6	-27.2	79.2	-27.7	-1	-5.6
261	CCTGAGACTGTGCGGTAGCA SEQ ID NO:1805	1.6	-27.6	76.9	-27.4	-1.8	-6.3
560	CATTCTCTTTCACAACTTCT SEQ ID NO:1806	1.6	-21.4	65.4	-23	0	-1
603	CAGCGTGGATTTAACCATTT SEQ ID NO:1807	1.6	-22.6	64.7	-23.6	-0.3	-5.5
1060	AGGAAGGGCTAAATATTTTA SEQ ID NO:1808	1.6	-18.2	56.5	-19.8	0	-6.6
1088	AATTAAATTCTAGAGAAGCT SEQ ID NO:1809	1.6	-16	52	-17.6	0	-5.8
1098	AAAAAAGCACAATTAAATTC SEQ ID NO:1810	1.6	-12.1	43.3	-13.7	0	-4.1
1446	AGGATGATAAATATGGGTAG SEQ ID NO:1811	1.6	-17.7	55.6	-19.3	0	-2.7
2	GTGGGAAGCAGCCGTGACCC SEQ ID NO:1812	1.7	-30.6	80.7	-31.4	-0.8	-5.4
8	TTGCTGGTGGGAAGCAGCCG SEQ ID NO:1813	1.7	-28.6	77.5	-27.4	-2.9	-8.4
11	TCTTTGCTGGTGGGAAGCAG SEQ ID NO:1814	1.7	-25.4	73.9	-25.2	-1.9	-6.4
1386	ATAAATATTTACCTTCATAC SEQ ID NO:1815	1.7	-16.1	52.2	-17.3	0	-7.9
1485	ACCATTTTCAACAAATAATA SEQ ID NO:1816	1.7	-15.8	50.6	-17	-0.1	-2.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1628	AGCACTTATGTTTAAATAAG SEQ ID NO:1817	1.7	-16.1	52.3	-16.6	-1.1	-6.6
1683	CAAACCTCCTAAAAACTTAT SEQ ID NO:1818	1.7	-17.5	53.1	-19.2	0	-1.3
1820	AAAATACTTCTGAGATATTT SEQ ID NO:1819	1.7	-15.2	50.4	-15.8	-1	-4.6
1863	GTAAATACTGAAATAATTCT SEQ ID NO:1820	1.7	-13.9	47.4	-14.4	-1.1	-4.8
421	CCTGTCACAGATGCCTGACT SEQ ID NO:1821	1.8	-27.1	75.9	-27.2	-1.7	-6.3
1305	AAGCTATTTATGGAAGTGTA SEQ ID NO:1822	1.8	-18.8	58.8	-20.6	0	-5.1
1375	CCTTCATACACACACAAACC SEQ ID NO:1823	1.8	-22.2	63	-24	0	-0.9
1116	CCCAAAGCCAAAAAAAAAAA SEQ ID NO:1824	1.9	-14.8	46.6	-16.7	0	-3.2
1167	CAAACATCTTACTTCCTTCA SEQ ID NO:1825	1.9	-21	62.6	-22.9	0	-1
1170	CTTCAAACATCTTACTTCCT SEQ ID NO:1826	1.9	-21.2	63.4	-23.1	0	-1
1174	TAAGCTTCAAACATCTTACT SEQ ID NO:1827	1.9	-18.6	57.7	-20.5	0	-6.8
1626	CACTTATGTTTAAATAAGGT SEQ ID NO:1828	1.9	-16.7	53.6	-17	-1.5	-7.1
1822	ATAAAATACTTCTGAGATAT SEQ ID NO:1829	1.9	-14.7	49.3	-16.6	0	-2.8
1855	TGAAATAATTCTTAAATAAG SEQ ID NO:1830	1.9	-11	41.6	-11.7	-1.1	-4.3
1878	AAGAATAAAATACAGGTAAA SEQ ID NO:1831	1.9	-12.1	43.4	-14	0	-3.6
1996	CTTGTTCTTTTTTATTGAAC SEQ ID NO:1832	1.9	-18	57.7	-18.8	-1	-4.9
503	GCTCCGTGAGAGAAACAAAT SEQ ID NO:1833	2	-21	60.4	-21.9	-1	-6.1
1172	AGCTTCAAACATCTTACTTC SEQ ID NO:1834	2	-20.1	62	-22.1	0	-4.3
1862	TAAATACTGAAATAATTCTT SEQ ID NO:1835	2	-12.8	45.1	-13.6	-1.1	-4.2
87	GGCACGAGGAGCGTGGTCAG SEQ ID NO:1836	2.1	-28.4	78.4	-27	-3.5	-9.3
169	GCTGCTTTTGCACTCACTGC SEQ ID NO:1837	2.1	-27.3	78.7	-27.3	-2.1	-7.4
424	CCCCCTGTCACAGATGCCTG SEQ ID NO:1838	2.1	-31.4	82.3	-32.4	-1	-5.3
844	ACACACATTTAACAAATCTA SEQ ID NO:1839	2.1	-16.4	52.2	-18.5	0	-2.7
1139	CTGGTTGTTTTATTTTGACT SEQ ID NO:1840	2.1	-20.6	63.9	-22.7	0	-2.8
420	CTGTCACAGATGCCTGACTG SEQ ID NO:1841	2.2	-25.1	72.2	-25.6	-1.7	-7
1138	TGGTTGTTTTATTTTGACTT SEQ ID NO:1842	2.2	-19.8	62.2	-22	0	-2.8
1443	ATGATAAATATGGGTAGGGA SEQ ID NO:1843	2.2	-18.9	57.9	-21.1	0	-2.7
1739	TTCCACCTATATTTTAAAGT SEQ ID NO:1844	2.2	-19.5	59.3	-21.7	0	-4.6
280	ACACTTCATGCCATCCATGC SEQ ID NO:1845	2.3	-26.6	74.3	-27.1	-1.8	-5
417	TCACAGATGCCTGACTGGCA SEQ ID NO:1846	2.3	-26.7	75	-25.6	-3.4	-9.2

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
848	ATACACACACATTTAACAAA SEQ ID NO:1847	2.3	-16	51	-18.3	0	-2.4
850	CTATACACACACATTTAACA SEQ ID NO:1848	2.3	-18	55.7	-20.3	0	-2.4
1163	CATCTTACTTCCTTCAGGGG SEQ ID NO:1849	2.3	-25.1	73.5	-26.9	-0.2	-4.7
1678	CTCCTAAAAACTTATTTTCA SEQ ID NO:1850	2.3	-17.4	54.4	-18.7	-0.9	-3.3
1373	TTCATACACACACAAACCAC SEQ ID NO:1851	2.4	-20.2	59.4	-22.6	0	-0.9
1483	CATTTTCAACAAATAATACT SEQ ID NO:1852	2.4	-14.7	48.7	-16.6	-0.1	-2.7
1575	AAATCCAGAGTGACTCCTAT SEQ ID NO:1853	2.4	-22.2	65	-23.9	-0.4	-5.5
78	AGCGTGGTCAGCAGCAAGAC SEQ ID NO:1854	2.5	-26.4	75.4	-27.3	-1.5	-7.3
260	CTGAGACTGTGCGGTAGCAA SEQ ID NO:1855	2.5	-24.9	70.9	-25.4	-2	-7
1171	GCTTCAAACATCTTACTTCC SEQ ID NO:1856	2.5	-22.1	65.6	-24.6	0	-2.8
1321	GAGGTGGCATACGTTAAAGC SEQ ID NO:1857	2.5	-22.8	66.1	-24.7	-0.3	-4.8
1453	CCTCAAGAGGATGATAAATA SEQ ID NO:1858	2.5	-18.3	56	-20.3	-0.1	-7.5
1562	CTCCTATAATTATGGATAAT SEQ ID NO:1859	2.5	-17.5	54.8	-19.3	-0.1	-9
1574	AATCCAGAGTGACTCCTATA SEQ ID NO:1860	2.5	-22.6	66.7	-24.4	-0.4	-5.5
422	CCCTGTCACAGATGCCTGAC SEQ ID NO:1861	2.6	-28.2	77.5	-29.3	-1.4	-5.9
561	GCATTCTCTTTCACAACTTC SEQ ID NO:1862	2.6	-22.3	67.8	-24.9	0	-3.4
721	AATTTGGATCTTCAAAAATT SEQ ID NO:1863	2.6	-15.1	49.6	-16.3	-1.3	-6.3
724	CACAATTTGGATCTTCAAAA SEQ ID NO:1864	2.6	-17.3	53.9	-19	-0.8	-5.8
706	AAATTACATGTACTTATGCT SEQ ID NO:1865	2.7	-17.8	55.9	-20	0	-7.7
713	TCTTCAAAAATTACATGTAC SEQ ID NO:1866	2.7	-15.5	50.9	-17.7	0	-7.7
1677	TCCTAAAAACTTATTTTCAT SEQ ID NO:1867	2.7	-16.5	52.6	-18.3	-0.7	-3.2
1821	TAAAATACTTCTGAGATATT SEQ ID NO:1868	2.7	-14.8	49.6	-17.5	0	-3.9
223	AGCGCACACTCGGCAGCAGC SEQ ID NO:1869	2.8	-30.3	81.5	-30.8	-2.3	-9.7
1297	TATGGAAGTGTATGTGTTTC SEQ ID NO:1870	2.8	-19.9	62.8	-22.7	0	-2.6
1627	GCACTTATGTTTAAATAAGG SEQ ID NO:1871	2.8	-17.3	54.7	-18.5	-1.5	-7.1
92	GTGCAGGCACGAGGAGCGTG SEQ ID NO:1872	2.9	-28.6	78.3	-28.4	-3.1	-11.5
289	CCCCGGGCCACACTTCATGC SEQ ID NO:1873	2.9	-32.7	83.1	-34.7	0	-9.7
410	TGCCTGACTGGCAGTTGCAG SEQ ID NO:1874	2.9	-27.9	78.6	-27.6	-3.2	-11.5
556	CTCTTTCACAACTTCTTCTC SEQ ID NO:1875	2.9	-22	67.8	-24.9	0	-0.7
839	CATTTAACAAATCTACATGC SEQ ID NO:1876	2.9	-17.1	53.7	-20	0	-5

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
1075	AGAAGCTACCTACCAAGGAA SEQ ID NO:1877	2.9	-22.4	63.9	-23.7	-1.6	-9.2
1440	ATAAATATGGGTAGGGAAGA SEQ ID NO:1878	2.9	-18.2	56.3	-21.1	0	-2.7
720	ATTTGGATCTTCAAAAATTA SEQ ID NO:1879	3	-15.5	50.7	-17.1	-1.3	-6.3
849	TATACACACACATTTAACAA SEQ ID NO:1880	3	-16.4	52.2	-19.4	0	-2.4
1087	ATTAAATTCTAGAGAAGCTA SEQ ID NO:1881	3.1	-16.4	53.2	-19.5	0	-5.8
1374	CTTCATACACACACAAACCA SEQ ID NO:1882	3.1	-20.9	60.7	-24	0	-0.9
1448	AGAGGATGATAAATATGGGT SEQ ID NO:1883	3.1	-18.6	57.5	-21.7	0	-2.7
1564	GACTCCTATAATTATGGATA SEQ ID NO:1884	3.1	-19	58.5	-21.4	-0.1	-9
1576	GAAATCCAGAGTGACTCCTA SEQ ID NO:1885	3.1	-22.8	66.4	-25.2	-0.4	-5.5
557	TCTCTTTCACAACTTCTTCT SEQ ID NO:1886	3.2	-22	67.8	-25.2	0	-0.7
1484	CCATTTTCAACAAATAATAC SEQ ID NO:1887	3.2	-15.8	50.6	-18.5	-0.1	-2.7
563	CAGCATTCTCTTTCACAACT SEQ ID NO:1888	3.3	-22.5	67.3	-25.8	0	-4.1
860	TTCAGTGTTACTATACACAC SEQ ID NO:1889	3.3	-19.9	62.3	-20.9	-2.3	-6.5
1864	GGTAAATACTGAAATAATTC SEQ ID NO:1890	3.3	-14.2	47.9	-16.9	-0.3	-7.3
1871	AAATACAGGTAAATACTGAA SEQ ID NO:1891	3.3	-14.6	48.4	-17.9	0	-4.1
1872	AAAATACAGGTAAATACTGA SEQ ID NO:1892	3.3	-14.6	48.4	-16.9	-0.9	-4.1
516	GATGCCATGTCATGCTCCGT SEQ ID NO:1893	3.4	-28.5	78.3	-31.4	-0.2	-4.6
562	AGCATTCTCTTTCACAACTT SEQ ID NO:1894	3.4	-21.9	66.4	-25.3	0	-4.1
841	CACATTTAACAAATCTACAT SEQ ID NO:1895	3.4	-16.2	51.7	-19.6	0	-2.7
1400	ATTTATAAAAATATATAAAT SEQ ID NO:1896	3.4	-8.5	36.9	-10.3	-1.5	-6.5
1442	TGATAAATATGGGTAGGGAA SEQ ID NO:1897	3.5	-18.2	56.1	-21.7	0	-2.7
1732	TATATTTTAAAGTTGACATG SEQ ID NO:1898	3.5	-14.8	49.7	-18.3	0	-4.7
419	TGTCACAGATGCCTGACTGG SEQ ID NO:1899	3.6	-25.4	72.8	-27.3	-1.7	-7.1
859	TCAGTGTTACTATACACACA SEQ ID NO:1900	3.6	-20.5	63.2	-21.8	-2.3	-6.5
1738	TCCACCTATATTTTAAAGTT SEQ ID NO:1901	3.6	-19.5	59.3	-23.1	0	-4.6
502	CTCCGTGAGAGAAACAAATC SEQ ID NO:1902	3.7	-19.6	58	-22.7	-0.3	-5
5	CTGGTGGGAAGCAGCCGTGA SEQ ID NO:1903	3.8	-28.5	77.6	-31.1	-1.1	-5.4
9	TTTGCTGGTGGGAAGCAGCC SEQ ID NO:1904	3.8	-27.9	78.2	-28.8	-2.9	-7.8
10	CTTTGCTGGTGGGAAGCAGC SEQ ID NO:1905	3.8	-26.8	76.6	-28.1	-2.5	-7.4
515	ATGCCATGTCATGCTCCGTG SEQ ID NO:1906	3.8	-27.9	76.8	-31.2	-0.2	-4.6

position	oligo	kcal/ mol total binding	kcal/ mol duplex form- ation	deg C Tm of Duplex	kcal/ mol target struc- ture	kcal/mol Intra- molecular oligo	kcal/mol Inter- molecular oligo
606	GATCAGCGTGGATTTAACCA SEQ ID NO:1907	3.9	-23.4	66.7	-26.5	-0.6	-5.9
1303	GCTATTTATGGAAGTGTATG SEQ ID NO:1908	3.9	-19.5	60.6	-23.4	0	-2.8
1563	ACTCCTATAATTATGGATAA SEQ ID NO:1909	3.9	-17.7	55.3	-20.9	-0.1	-9
714	ATCTTCAAAAATTACATGTA SEQ ID NO:1910	4	-15.3	50.4	-18.8	0	-7.5
1449	AAGAGGATGATAAATATGGG SEQ ID NO:1911	4	-16.7	52.8	-20.7	0	-2.7
1866	CAGGTAAATACTGAAATAAT SEQ ID NO:1912	4	-14.4	48	-18.4	0	-3.8
6	GCTGGTGGGAAGCAGCCGTG SEQ ID NO:1913	4.1	-29.7	80.5	-31.6	-2.2	-8.4
518	CAGATGCCATGTCATGCTCC SEQ ID NO:1914	4.1	-27.2	76.6	-30.8	-0.1	-4.4
1099	AAAAAAAGCACAATTAAATT SEQ ID NO:1915	4.1	-11	41.2	-15.1	0	-4.1
1865	AGGTAAATACTGAAATAATT SEQ ID NO:1916	4.1	-13.8	47	-17.9	0	-3.8
600	CGTGGATTTAACCATTTCCT SEQ ID NO:1917	4.2	-23.4	66.2	-26.7	-0.8	-4.8
609	CGGGATCAGCGTGGATTTAA SEQ ID NO:1918	4.2	-23.7	66.7	-27.9	0	-5.7
1733	CTATATTTTAAAGTTGACAT SEQ ID NO:1919	4.2	-15.7	51.6	-19.9	0	-4.6
719	TTTGGATCTTCAAAAATTAC SEQ ID NO:1920	4.3	-15.7	51.2	-19.1	-0.8	-5.6
1304	AGCTATTTATGGAAGTGTAT SEQ ID NO:1921	4.3	-19.5	60.9	-23.8	0	-4.3
1441	GATAAATATGGGTAGGGAAG SEQ ID NO:1922	4.3	-18.2	56.3	-22.5	0	-2.2
843	CACACATTTAACAAATCTAC SEQ ID NO:1923	4.4	-16.4	52.2	-20.8	0	-2.5
3	GGTGGGAAGCAGCCGTGACC SEQ ID NO:1924	4.5	-29.8	79.9	-33.6	-0.4	-5.4
517	AGATGCCATGTCATGCTCCG SEQ ID NO:1925	4.5	-27.3	75.3	-31.3	-0.2	-4.6
707	AAAATTACATGTACTTATGC SEQ ID NO:1926	4.6	-16.2	52.2	-20.3	0	-7.5
840	ACATTTAACAAATCTACATG SEQ ID NO:1927	4.6	-15.5	50.5	-20.1	0	-4.7
1103	AAAAAAAAAAAGCACAATTA SEQ ID NO:1928	4.6	-9.5	38.6	-14.1	0	-4.1
1176	CATAAGCTTCAAACATCTTA SEQ ID NO:1929	4.6	-18.2	56.5	-22.8	0	-6.8
1302	CTATTTATGGAAGTGTATGT SEQ ID NO:1930	4.6	-18.9	59.5	-23.5	0	-1.8
1676	CCTAAAAACTTATTTTCATA SEQ ID NO:1931	4.7	-15.8	51	-19.5	-0.9	-3.3
564	GCAGCATTCTCTTTCACAAC SEQ ID NO:1932	4.8	-23.4	69.6	-28.2	0	-4.7
842	ACACATTTAACAAATCTACA SEQ ID NO:1933	4.8	-16.4	52.2	-21.2	0	-2.7
718	TTGGATCTTCAAAAATTACA SEQ ID NO:1934	4.9	-16.3	52.1	-21.2	0	-5
1104	AAAAAAAAAAAAGCACAATT SEQ ID NO:1935	4.9	-9.1	38	-14	0	-4.1
1450	CAAGAGGATGATAAATATGG SEQ ID NO:1936	4.9	-16.2	51.7	-21.1	0	-2.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intra-molecular oligo	kcal/mol Inter-molecular oligo
75	GTGGTCAGCAGCAAGACGCT SEQ ID NO:1937	5	-27.3	77.1	-30.8	-1.4	-8.5
91	TGCAGGCACGAGGAGCGTGG SEQ ID NO:1938	5	-28.6	77.4	-30.1	-3.5	-11.6
1954	AACAAAACCTAACAGCTTAT SEQ ID NO:1939	5	-17.6	53.7	-22.6	0	-4.5
1115	CCAAAGCCAAAAAAAAAAAA SEQ ID NO:1940	5.2	-12.1	42.5	-17.3	0	-2.4
1870	AATACAGGTAAATACTGAAA SEQ ID NO:1941	5.2	-14.6	48.4	-18.8	-0.9	-4.1
77	GCGTGGTCAGCAGCAAGACG SEQ ID NO:1942	5.3	-27.2	74.9	-31.6	-0.7	-7.7
414	CAGATGCCTGACTGGCAGTT SEQ ID NO:1943	5.4	-26.7	75.7	-28.5	-3.6	-8.6
423	CCCCTGTCACAGATGCCTGA SEQ ID NO:1944	5.4	-30	80.3	-33.9	-1.4	-5.7
602	AGCGTGGATTTAACCATTTC SEQ ID NO:1945	5.5	-22.3	65	-26.9	-0.8	-5.5
708	AAAAATTACATGTACTTATG SEQ ID NO:1946	5.5	-13.7	46.9	-18.7	0	-7.7
1100	AAAAAAAAGCACAATTAAAT SEQ ID NO:1947	5.5	-10.2	39.8	-15.7	0	-4.1
1955	AAACAAAACCTAACAGCTTA SEQ ID NO:1948	5.5	-16.9	52.1	-22.4	0	-4.5
413	AGATGCCTGACTGGCAGTTG SEQ ID NO:1949	5.6	-26	74.4	-28	-3.6	-8.6
76	CGTGGTCAGCAGCAAGACGC SEQ ID NO:1950	5.7	-27.2	74.9	-31.4	-1.4	-8.5
858	CAGTGTTACTATACACACAC SEQ ID NO:1951	5.7	-20.3	62.3	-23.7	-2.3	-6.5
1105	AAAAAAAAAAAAAGCACAAT SEQ ID NO:1952	5.8	-8.3	36.7	-14.1	0	-4.1
601	GCGTGGATTTAACCATTTCC SEQ ID NO:1953	5.9	-24.3	68.3	-29.3	-0.8	-6.2
1867	ACAGGTAAATACTGAAATAA SEQ ID NO:1954	5.9	-14.6	48.4	-19.5	-0.9	-4.1
411	ATGCCTGACTGGCAGTTGCA SEQ ID NO:1955	6	-27.9	78.3	-30.3	-3.6	-11.9
607	GGATCAGCGTGGATTTAACC SEQ ID NO:1956	6	-23.9	68.1	-29.9	0	-5.7
415	ACAGATGCCTGACTGGCAGT SEQ ID NO:1957	6.1	-26.8	75.9	-29.8	-3.1	-9.8
1102	AAAAAAAAAAGCACAATTAA SEQ ID NO:1958	6.1	-9.5	38.6	-15.6	0	-4.1
1734	CCTATATTTTAAAGTTGACA SEQ ID NO:1959	6.1	-17.7	55.5	-23.8	0	-4.6
1086	TTAAATTCTAGAGAAGCTAC SEQ ID NO:1960	6.2	-16.6	53.8	-22.8	0	-5.8
1166	AAACATCTTACTTCCTTCAG SEQ ID NO:1961	6.3	-20.3	61.6	-26.6	0	-1.6
412	GATGCCTGACTGGCAGTTGC SEQ ID NO:1962	6.4	-27.8	78.6	-30.6	-3.6	-9.7
717	TGGATCTTCAAAAATTACAT SEQ ID NO:1963	6.6	-16.2	51.9	-22.8	0	-5
1675	CTAAAAACTTATTTTCATAC SEQ ID NO:1964	6.7	-14	47.7	-19.7	-0.9	-3.3
1076	GAGAAGCTACCTACCAAGGA SEQ ID NO:1965	6.8	-23.7	67.2	-28.9	-1.6	-9.2
657	GTGTGTTGAACAATCACGAA SEQ ID NO:1966	6.9	-19.8	59.1	-25.3	-1.3	-8.7

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
715	GATCTTCAAAAATTACATGT SEQ ID NO:1967	6.9	-16.2	52.1	-23.1	0	-6.3
1868	TACAGGTAAATACTGAAATA SEQ ID NO:1968	6.9	-15	49.5	-20.9	-0.9	-4.1
1880	TCAAGAATAAAATACAGGTA SEQ ID NO:1969	7.1	-14.6	48.6	-21.7	0	-3.4
656	TGTGTTGAACAATCACGAAA SEQ ID NO:1970	7.3	-17.9	54.5	-23.8	-1.3	-8.7
1164	ACATCTTACTTCCTTCAGGG SEQ ID NO:1971	7.4	-24.1	71.4	-31.5	0	-4.7
1886	CCAACTTCAAGAATAAAATA SEQ ID NO:1972	7.4	-14.8	48.3	-22.2	0	-3.5
1106	AAAAAAAAAAAAAAGCACAA SEQ ID NO:1973	7.5	-7.6	35.7	-15.1	0	-4.1
1101	AAAAAAAAAGCACAATTAAA SEQ ID NO:1974	7.6	-9.5	38.6	-17.1	0	-4.1
1881	TTCAAGAATAAAATACAGGT SEQ ID NO:1975	7.6	-15	49.4	-22.6	0	-2.9
1884	AACTTCAAGAATAAAATACA SEQ ID NO:1976	7.6	-13	45.2	-20.6	0	-3.5
416	CACAGATGCCTGACTGGCAG SEQ ID NO:1977	7.7	-26.3	73.6	-30.4	-3.6	-9.8
608	GGGATCAGCGTGGATTTAAC SEQ ID NO:1978	8.2	-23.1	67	-31.3	0	-5.3
1107	AAAAAAAAAAAAAAAGCACA SEQ ID NO:1979	8.3	-7.6	35.7	-15.9	0	-4.1
1885	CAACTTCAAGAATAAAATAC SEQ ID NO:1980	8.4	-13	45.2	-21.4	0	-3.5
716	GGATCTTCAAAAATTACATG SEQ ID NO:1981	8.5	-16.2	51.9	-24.7	0	-5
1451	TCAAGAGGATGATAAATATG SEQ ID NO:1982	8.6	-15.4	50.4	-24	0	-2.7
1879	CAAGAATAAAATACAGGTAA SEQ ID NO:1983	8.6	-13.5	46.1	-22.1	0	-3.6
1735	ACCTATATTTTAAAGTTGAC SEQ ID NO:1984	8.8	-17.2	54.7	-26	0	-4.6
1883	ACTTCAAGAATAAAATACAG SEQ ID NO:1985	8.8	-13.7	46.7	-22.5	0	-3.5
1452	CTCAAGAGGATGATAAATAT SEQ ID NO:1986	8.9	-16.3	52.3	-25.2	0	-3.9
4	TGGTGGGAAGCAGCCGTGAC SEQ ID NO:1987	9.2	-27.8	76.3	-35.8	-1.1	-4.6
1114	CAAAGCCAAAAAAAAAAAAA SEQ ID NO:1988	9.3	-9.4	38.4	-18.7	0	-3.2
1165	AACATCTTACTTCCTTCAGG SEQ ID NO:1989	9.3	-22.2	66.4	-31.5	0	-4.1
1882	CTTCAAGAATAAAATACAGG SEQ ID NO:1990	9.8	-14.7	48.6	-24.5	0	-3.5
1109	CCAAAAAAAAAAAAAAAGCA SEQ ID NO:1991	10.3	-9.4	38.4	-19.7	0	-4.1
1108	CAAAAAAAAAAAAAAAGCAC SEQ ID NO:1992	10.5	-7.6	35.7	-18.1	0	-4.1
1869	ATACAGGTAAATACTGAAAT SEQ ID NO:1993	10.9	-15.3	50	-25.2	-0.9	-4.1
1113	AAAGCCAAAAAAAAAAAAAA SEQ ID NO:1994	11.6	-8	36.3	-19.6	0	-3.2
1110	GCCAAAAAAAAAAAAAAAGC SEQ ID NO:1995	11.7	-10.5	40.1	-22.2	0	-2.8
1175	ATAAGCTTCAAACATCTTAC SEQ ID NO:1996	12.4	-17.7	55.8	-30.1	0	-6.8

position	oligo	kcal/mol total binding	kcal/mol duplex formation	deg C Tm of Duplex	kcal/mol target structure	kcal/mol Intramolecular oligo	kcal/mol Intermolecular oligo
1737	CCACCTATATTTTAAAGTTG SEQ ID NO:1997	13	-19.1	57.9	-32.1	0	-4.6
1736	CACCTATATTTTAAAGTTGA SEQ ID NO:1998	14.9	-17.7	55.5	-32.6	0	-4.6
1112	AAGCCAAAAAAAAAAAAAAA SEQ ID NO:1999	16.6	-8	36.3	-24.6	0	-3.2
1111	AGCCAAAAAAAAAAAAAAAG SEQ ID NO:2000	17.1	-8.7	37.4	-25.8	0	-3.2

Example 15

Western blot analysis of ESM-1 protein levels

[00230] Western blot analysis (immunoblot analysis) is carried out using standard methods. Cells are harvested 16-20 h after oligonucleotide treatment, washed once with PBS, suspended in Laemmli buffer (100 ul/well), boiled for 5 minutes and loaded on a 16% SDS-PAGE gel. Gels are run for 1.5 hours at 150 V, and transferred to membrane for western blotting. Appropriate primary antibody directed to ESM-1 is used, with a radiolabeled or fluorescently labeled secondary antibody directed against the primary antibody species. Bands are visualized using a PHOSPHORIMAGER™ (Molecular Dynamics, Sunnyvale CA).

WHAT IS CLAIMED IS:

1. An antisense compound 8 to 30 nucleobases in length targeted to a nucleic acid molecule encoding ESM-1, wherein said antisense compound specifically hybridizes with and inhibits the expression of ESM-1.

2. The antisense compound of claim 1 which is an antisense oligonucleotide.

3. The antisense oligonucleotide of claim 2 comprising a nucleic acid sequence selected from the group consisting of at least eight contiguous bases of SEQ ID NO:1 – SEQ ID NO:2000.

4. The antisense oligonucleotide of claim 2 comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1 – SEQ ID NO:2000.

5. The antisense compound of claim 2, 3, or 4 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

6. The antisense compound of claim 5 wherein the modified internucleoside linkage is a phosphorothioate linkage.

7. The antisense compound of claim 2, 3, or 4 wherein the antisense oligonucleotide comprises at least one modified sugar moiety.

8. The antisense compound of claim 7 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

9. The antisense compound of claim 2, 3, or 4 wherein the antisense oligonucleotide comprises at least one modified nucleobase.

10. The antisense compound of claim 9 wherein the modified nucleobase is a 5-methylcytosine.

11. The antisense compound of claim 2, 3, or 4 wherein the antisense oligonucleotide is a chimeric oligonucleotide.

12. A composition comprising the antisense compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

13. The composition of claim 12 further comprising a colloidal dispersion system.

14. The composition of claim 13 wherein the antisense compound is an antisense oligonucleotide.

15. A method of inhibiting the expression of ESM-1 in cells or tissues comprising contacting said cells or tissues with the antisense compound of claim 1 so that expression of ESM-1 is inhibited.

16. A method of treating a human having a disease or condition associated with ESM-1 comprising administering to said animal a therapeutically or prophylactically effective amount of the antisense compound of claim 1 so that expression of ESM-1 is inhibited.

17. The method of claim 16 wherein the disease or condition is diabetes.

18. The method of claim 16 wherein the disease or condition is an immunological disorder.

19. The method of claim 16 wherein the disease or condition is a cardiovascular disorder.

20. The method of claim 16 wherein the disease or condition is a neurologic disorder.

21. The method of claim 16 wherein the disease or condition is ischemia/reperfusion injury.

22. The method of claim 16 wherein the disease or condition is any form of cancer.

23. The method of claim 16 wherein the disease or condition is an angiogenic disorder.

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Figure 1

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C K D C P Y G T F G M D C R E T C N C Q

363 tgcaaagactgtccctacggcaccttcgggatggattgcagagagacctgcaactgccag 422

S G I C D R G T G K C L K F P F F Q Y S

423 tcaggcatctgtgacagggggacgggaaaatgcctgaaattccccttcttccaatattca 482

V T K S S N R F V S L T E H D M A S G D

483 gtaaccaagtcttccaacagatttgtttctctcacggagcatgacatggcatctggagat 542

G N I V R E E V V K E N A A G S P V M R

543 ggcaatattgtgagagaagaagttgtgaaagagaatgctgccgggtctcccgtaatgagg 602

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Figure 1 cont.

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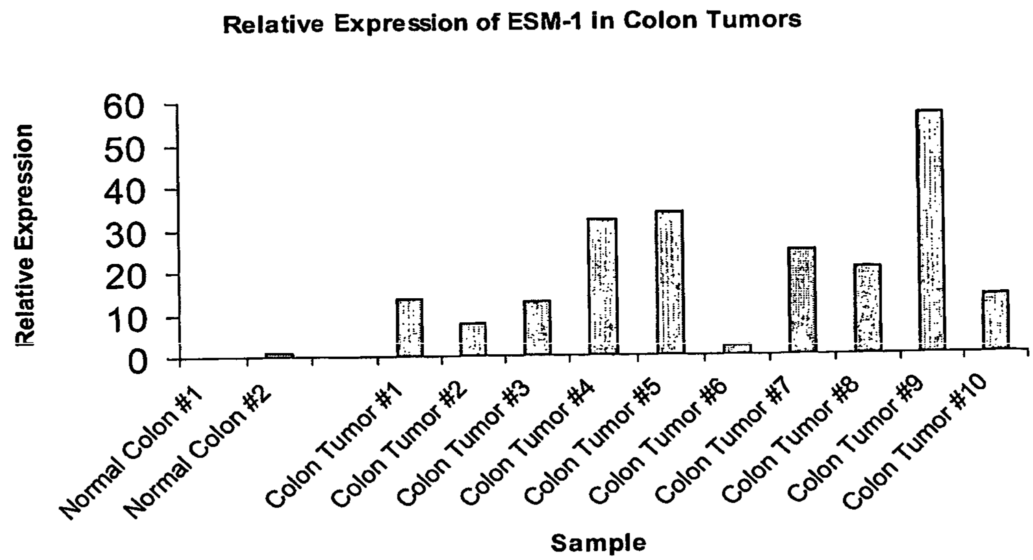
Figure 2



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Weinstein, Edward J

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Cys Tyr Arg Thr Val Ser Gly Met Asp Gly Met Lys Cys Gly Pro Gly
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